UNITED STATES PATENT
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FOR

WATER SOLUBLE THIAZOLYL PEPTIDE DERIVATIVES

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CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial Number 60/225,598 filed on August 15, 2000.

FIELD OF THE INVENTION

This invention relates to novel thiazolyl peptide compounds useful for the treatment of serious bacterial infections and suitable for both oral and, particularly, parenteral administration. This invention also relates to a pharmaceutical composition, especially an antibacterial composition, which comprises the novel thiazolyl peptide derivative as an active ingredient. The invention also provides a method for treating serious bacterial infections by administering to a mammal in need thereof said thiazolyl peptide compounds or a pharmaceutical composition of the thiazolyl peptide compounds.

BACKGROUND OF THE INVENTION

Multidrug-resistant strains of many clinically important pathogenic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and *Enterococci* strains are becoming a worldwide health problem. There is an urgent need to discover new agents to treat patients infected with multidrug-resistant bacteria. Many thiazolyl peptide antibiotics possess potent antimicrobial activity against Gram-positive bacteria, including multidrug-resistant strains, however many of these compounds have poor water solubility. The poor water solubility possessed by many of the thiazolyl peptide antibiotics poses a number of serious limitations to their method of administration and use as therapeutic agents. It is therefore desirable to have thiazolyl peptide antibiotics which are water soluble and can be readily administered while maintaining potent antimicrobial activity. Novel

thiazolyl peptide antibiotics, having inhibitory activity at the nanomolar level against Gram-positive bacteria, have been discovered. The thiazolyl peptide compounds described herein exhibit potent antimicrobial activity against Gram-positive bacteria *in vitro*, and exhibit *in vivo* efficacy in a systemic *Staph. aureus* infection model in animals. Many of the compounds of the present invention are water-soluble antibiotics, generally with a solubility of 2-10 mg/mL in water at a pH of 2-4. Many of the compounds are suitable for parenteral use in the treatment of serious bacterial infections in mammals, and more particularly, in humans.

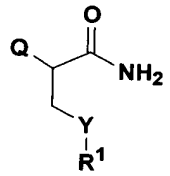
BACKGROUND OF THE INVENTION

The novel thiazolyl peptide antibiotics of this invention are derived from thiazolyl peptide antibiotics such as the nocathiacins described by J. E. Leet *et al* in US 6,218,398 (issued 4/17/2001), PCT Appl. WO 00/03722 (published 1/27/2000); PCT Appl. WO 00/14100 and Sasaki, T. *et al.*, *J. of Antibiotics* **51**, No. 8, pp. 715-721 (1998); and nosiheptide (Prange, T. *et al.*, *J. Am Chem Soc.* **1977**, *99*, 6418; Benazet, F. *et al.*, *Experientia* **1980**, *36*, 414; Floss, H.G. et al., *J. Am Chem Soc.***1993**, *115*, 7557). Other novel water-soluble thiazolyl peptide antibiotics may be derived from thiazolyl peptide antibiotics such as Antibiotic S-54832A (Keller-Juslen, C. *et al.*, U.S. Patent No. 4,478,831, 1984); thiostrepton (Anderson, B. *et al.*, *Nature* **1970**, *225*, 233-235; U.S. Patent 2,982,689, 1961 and U.S. Patent 2,982,698, 1961); thiopeptin; methylsulfomycin I (Kumar, V.; Kenia, J.; Mukhopadhyay, T.; Nadkarni, S.R. *J. Nat. Prod.* **1999**, *62*, 1562-1564; GE37468 (Stella, S. *et al J. of Antibiotics* **1995**, 48(8), 780-786); Sch 40832 (Puar, M.S. *et al.* in *J. of Antibiotics* **1998**, *51(2)*, 221-224); promothiocins (Yun, B.S. et al. *J. Antibiotics* **1994**, *47*, 510-514 and Bagley, M.C. et al. *J. Am. Chem. Soc.* **2000**, *122*, 3301-3313) according to the methods described herein.

SUMMARY OF THE INVENTION

This invention relates to novel thiazolyl peptide compounds, pharmaceutical compositions which contain the novel thiazolyl peptide compounds, and methods of treating mammals which have or are susceptible to serious bacterial infections.

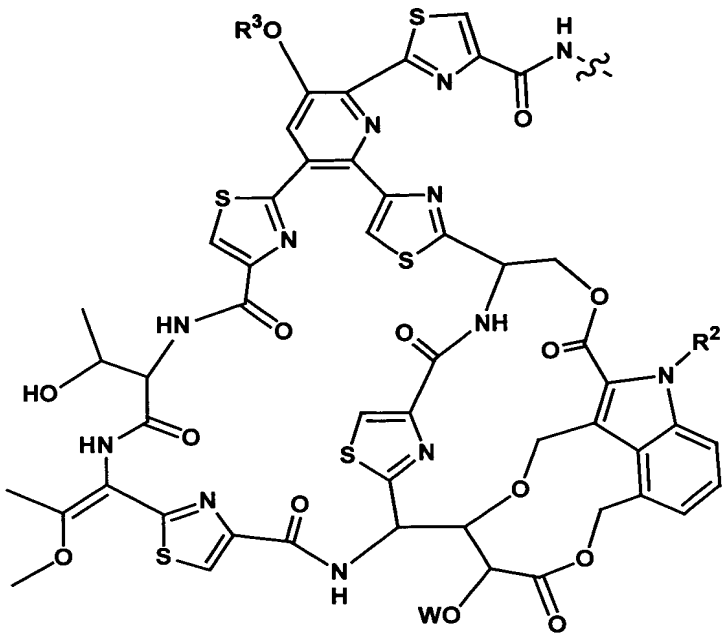
Accordingly, compounds of Formula I, including pharmaceutically acceptable salts thereof, have been discovered which possess potent antibiotic activity, particularly in inhibiting the growth of Gram-positive bacteria and mycobacteria. The compounds are of Formula I



I

wherein:

Q is a residue of a thiazolyl peptide antibiotic selected from:



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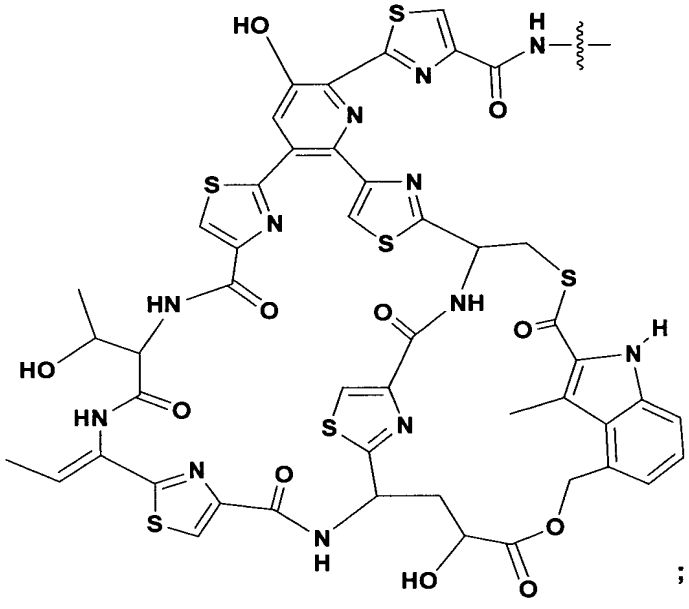

;

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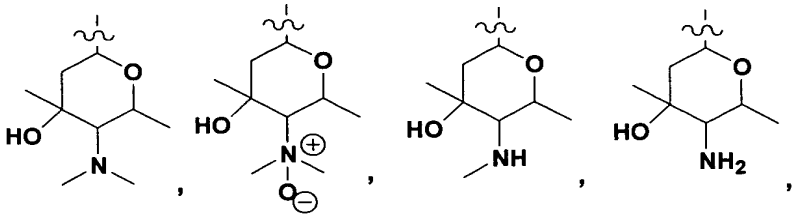
Y is NR or $S(O)_m$;

m is 0, 1, or 2;

W is selected from the group consisting of hydrogen,



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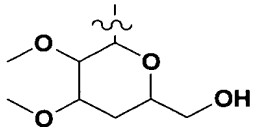


;

R is selected from the group consisting of hydrogen, hydroxy, C_{1-6}alkoxy, $-[(CH_2)_2O]_p(CH_2)_2R^4$, $-C(O)C_{1-6}$alkyl, $-C(O)C_{1-6}$alkylCO_2H, $-C(O)NHC_{1-6}$alkyl and C_{1-8}alkyl, in which said C_{1-8}alkyl is optionally substituted by one to six hydroxy and optionally substituted by one to two same or different substituents selected from the group consisting of (a)-(h):

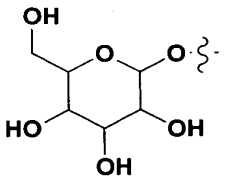
(a) CO_2R^5;

(b) SO_3H;

(c) NR^6R^7;

(d) heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl, and in which said heteroaryl is optionally substituted with one or two same or different nitro or C_{1-4}alkyl;

(e) phenyl, in which said phenyl is optionally substituted with one to three C_{1-4}alkoxy or optionally substituted with one



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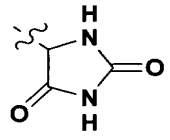
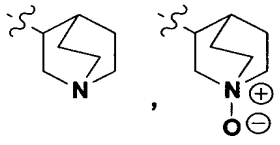


;

(g) C_{1-4}alkoxy; and

(h) –C(O)NH-heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl;

R^1 is selected from the group consisting of:



, hydrogen, $-[(CH_2)_2O]_{p'}(CH_2)_2R^{4'}$ and C_{1-8}alkyl, in which said C_{1-8}alkyl is optionally substituted by one to six hydroxy and optionally substituted by one to two same or different substituents selected from the group consisting of (a)-(h):

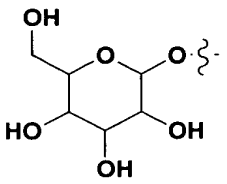
(a) $CO_2R^{5'}$;

(b) SO_3H;

(c) $NR^{6'}R^{7'}$

(d) heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl, and in which said heteroaryl is optionally substituted with one or two same or different nitro or C_{1-4}alkyl;

(e) phenyl, in which said phenyl is optionally substituted with one to three C_{1-4}alkoxy or optionally substituted with one



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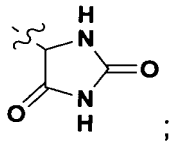
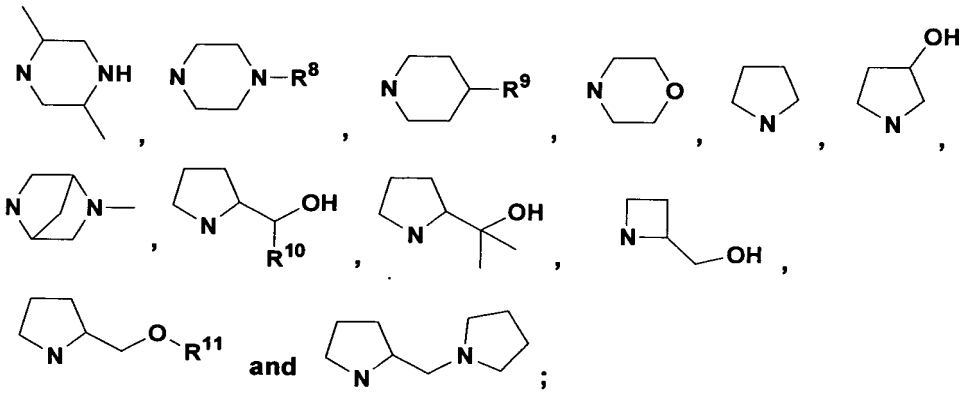


;

(g) C_{1-4}alkoxy; and

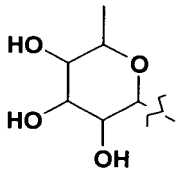
(h) –C(O)NH-heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl;

or R and R^1 together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of:



R^2 is selected from the group consisting of hydrogen, hydroxy, -OC(O) C_{1-6}alkyl and -OC(O)NHC_{1-6}alkyl;

R^3 is hydrogen or



;

p and p' are each independently selected from the group consisting of 1, 2 and 3;

R^4 and $R^{4'}$ are each independently selected from the group consisting of hydroxy, amino and C_{1-4}alkoxy;

R^5 and $R^{5'}$ are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl and phenylmethyl;

R^6, $R^{6'}$, R^7 and $R^{7'}$ are each independently selected from the group consisting of hydrogen, $-C(O)C_{1-6}$alkyl, pyridinyl and C_{1-6}alkyl, in which said C_{1-6}alkyl is optionally substituted with one hydroxy, amino, C_{1-4}alkylamino, or di(C_{1-4}alkyl)amino,

or R^6 and R^7 taken together with the nitrogen to which they are attached, or $R^{6'}$ and $R^{7'}$ taken together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of succinimid-1-yl, pyrrolidin-2-one-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholin-4-yl, piperazin-1-yl and 4-methylpiperazin-1-yl;

R^8 is selected from the group consisting of C_{1-6}alkyl, $-C(O)C_{1-6}$alkyl, $-[(CH_2)_2O]_q(CH_2)_2R^{8'}$, pyridinyl and pyrimidinyl, in which said C_{1-6}alkyl is optionally substituted with one di(C_{1-4}alkyl)amino, morpholin-4-yl, CO_2H, $-CO_2C_{1-4}$alkyl, tri(C_{1-4}alkoxy)phenyl and di(C_{1-4}alkoxy)pyrimidinyl;

q is 1, 2 or 3;

$R^{8'}$ is selected from the group consisting of hydroxy, amino and C_{1-4}alkoxy;

R^9 is hydrogen or hydroxy;

R^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl and 1-methyl-1H-imidazol-2-yl; and

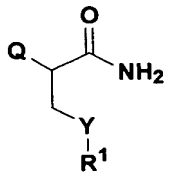
R^{11} is C_{1-4}alkyl or pyridinyl.

Pharmaceutical compositions containing a compound of Formula I in addition to a pharmaceutically acceptable carrier, adjuvant or diluent are within the scope of this invention. Methods of treating or preventing bacterial or mycobacterial infections in a mammal in need thereof by administering a compound of Formula I to said mammal are also within the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The description of the invention herein should be construed in congruity with the laws and principals of chemical bonding. An embodiment or aspect which depends from another embodiment or aspect, will describe only the variables having values and provisos that differ from the embodiment or aspect from which it depends. Thus, for example, an embodiment which reads "the compound of formula I according to the n^{th} aspect of the invention, wherein R^1 is C_{1-8}alkyl should be read to include all remaining variables with values defined in the n^{th} aspect and should be read to further include all the provisos, unless otherwise indicated, pertaining to each and every variable in the n^{th} aspect.

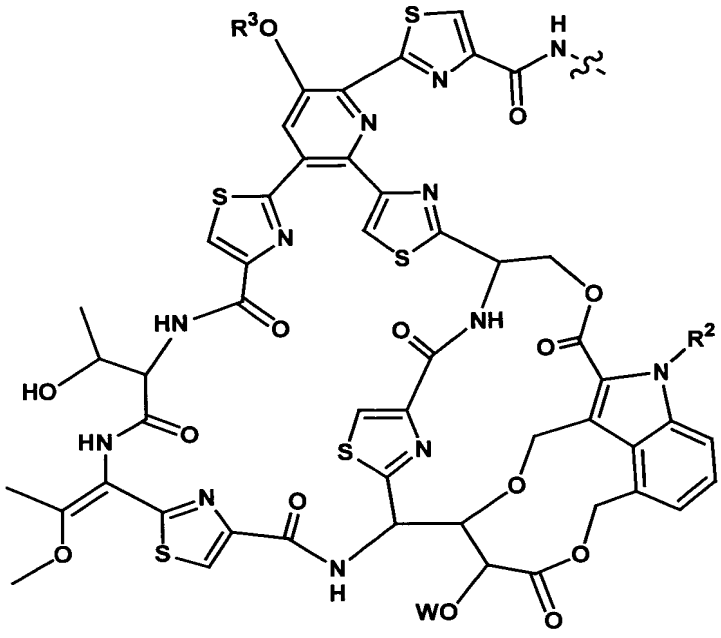
A first embodiment of a first aspect of the present invention is a compound of Formula I, including pharmaceutically acceptable salts thereof,



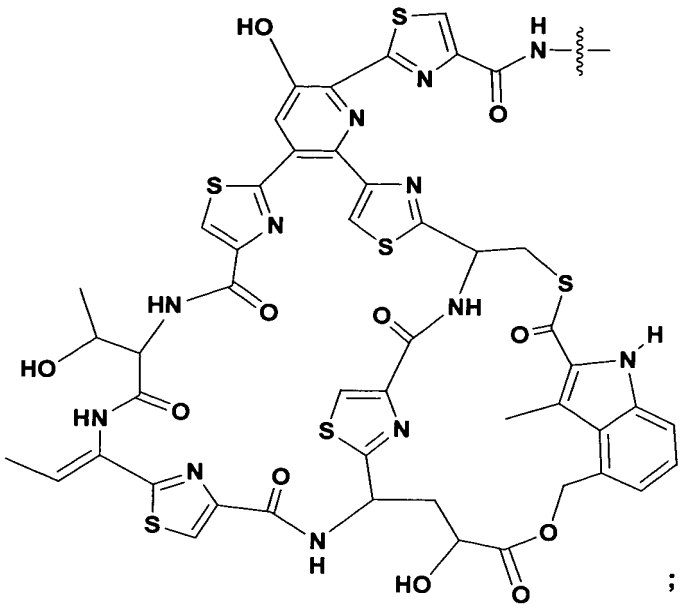
I

wherein:

Q is a residue of a thiazolyl peptide antibiotic selected from:



, or

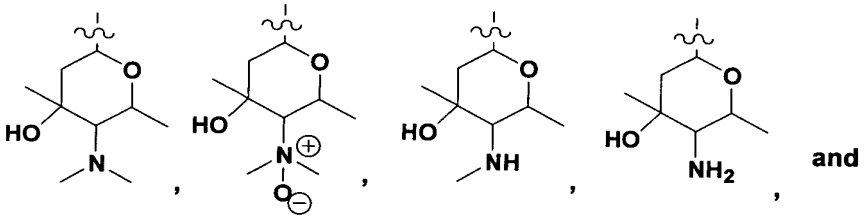


;

Y is NR or $S(O)_m$;

m is 0, 1, or 2;

W is selected from the group consisting of hydrogen,



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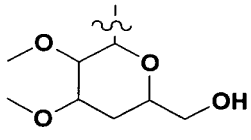


;

R is selected from the group consisting of hydrogen, hydroxy, C_{1-6}alkoxy, $-[(CH_2)_2O]_p(CH_2)_2R^4$, $-C(O)C_{1-6}$alkyl, $-C(O)C_{1-6}$alkylCO_2H, $-C(O)NHC_{1-6}$alkyl and C_{1-8}alkyl, in which said C_{1-8}alkyl is optionally substituted by one to six

hydroxy and optionally substituted by one to two same or different substituents selected from the group consisting of (a)-(h):

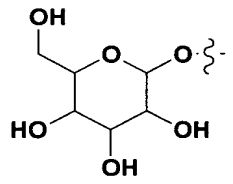
(a) CO_2R^5;

(b) SO_3H;

(c) NR^6R^7;

(d) heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl, and in which said heteroaryl is optionally substituted with one or two same or different nitro or C_{1-4}alkyl;

(e) phenyl, in which said phenyl is optionally substituted with one to three C_{1-4}alkoxy or optionally substituted with one



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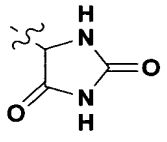
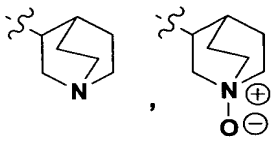


;

(g) C_{1-4}alkoxy; and

(h) –C(O)NH-heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl;

R^1 is selected from the group consisting of:



hydrogen, $-[(CH_2)_2O]_{p'}(CH_2)_2R^{4'}$ and C_{1-8}alkyl, in which said C_{1-8}alkyl is optionally substituted by one to six hydroxy and optionally substituted by one to two same or different substituents selected from the group consisting of (a)-(h):

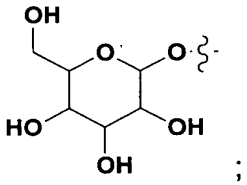
(a) $CO_2R^{5'}$;

(b) SO_3H;

(c) $NR^{6'}R^{7'}$

(d) heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl, and in which said heteroaryl is optionally substituted with one or two same or different nitro or C_{1-4}alkyl;

(e) phenyl, in which said phenyl is optionally substituted with one to three C_{1-4}alkoxy or optionally substituted with one



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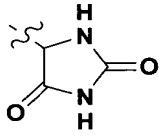
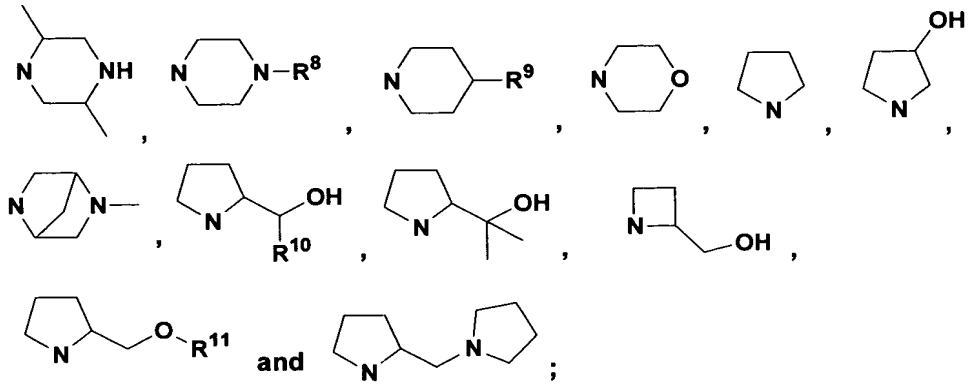


;

(g) C_{1-4}alkoxy; and

(h) –C(O)NH-heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl;

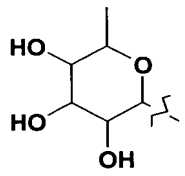
or R and R^1 together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of:



;

R^2 is selected from the group consisting of hydrogen, hydroxy, -OC(O) C_{1-6}alkyl and -OC(O)NHC_{1-6}alkyl;

R^3 is hydrogen or



;

p and p' are each independently selected from the group consisting of 1, 2 and 3;

R^4 and $R^{4'}$ are each independently selected from the group consisting of hydroxy, amino and C_{1-4}alkoxy;

R^5 and $R^{5'}$ are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl and phenylmethyl;

R^6, $R^{6'}$, R^7 and $R^{7'}$ are each independently selected from the group consisting of hydrogen, -C(O)C_{1-6}alkyl, pyridinyl and C_{1-6}alkyl, in which said

C_{1-6}alkyl is optionally substituted with one hydroxy, amino, C_{1-4}alkylamino, or di(C_{1-4}alkyl)amino,

or R^6 and R^7 taken together with the nitrogen to which they are attached, or $R^{6'}$ and $R^{7'}$ taken together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of succinimid-1-yl, pyrrolidin-2-one-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholin-4-yl, piperazin-1-yl and 4-methylpiperazin-1-yl;

R^8 is selected from the group consisting of C_{1-6}alkyl, -C(O)C_{1-6}alkyl, -$[(CH_2)_2O]_q(CH_2)_2R^{8'}$, pyridinyl and pyrimidinyl, in which said C_{1-6}alkyl is optionally substituted with one di(C_{1-4}alkyl)amino, morpholin-4-yl, CO_2H, -CO_2C_{1-4}alkyl, tri(C_{1-4}alkoxy)phenyl and di(C_{1-4}alkoxy)pyrimidinyl;

q is 1, 2 or 3;

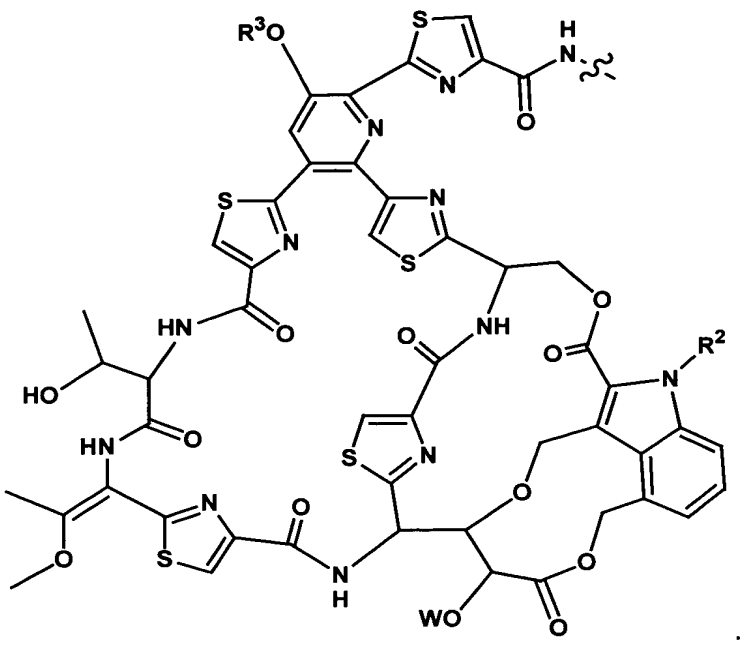
$R^{8'}$ is selected from the group consisting of hydroxy, amino and C_{1-4}alkoxy;

R^9 is hydrogen or hydroxy;

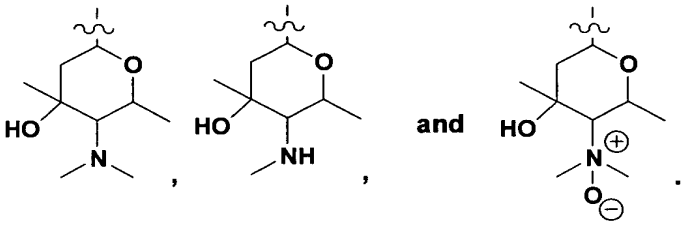
R^{10} is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl and 1-methyl-1H-imidazol-2-yl; and

R^{11} is C_{1-4}alkyl or pyridinyl.

A second embodiment of a first aspect of the present invention is compound of the first embodiment, including pharmaceutically acceptable salts thereof, wherein Q is



A third embodiment of a first aspect of the present invention is a compound of the second embodiment, including pharmaceutically acceptable salts thereof, wherein W is selected from the group consisting of hydrogen,

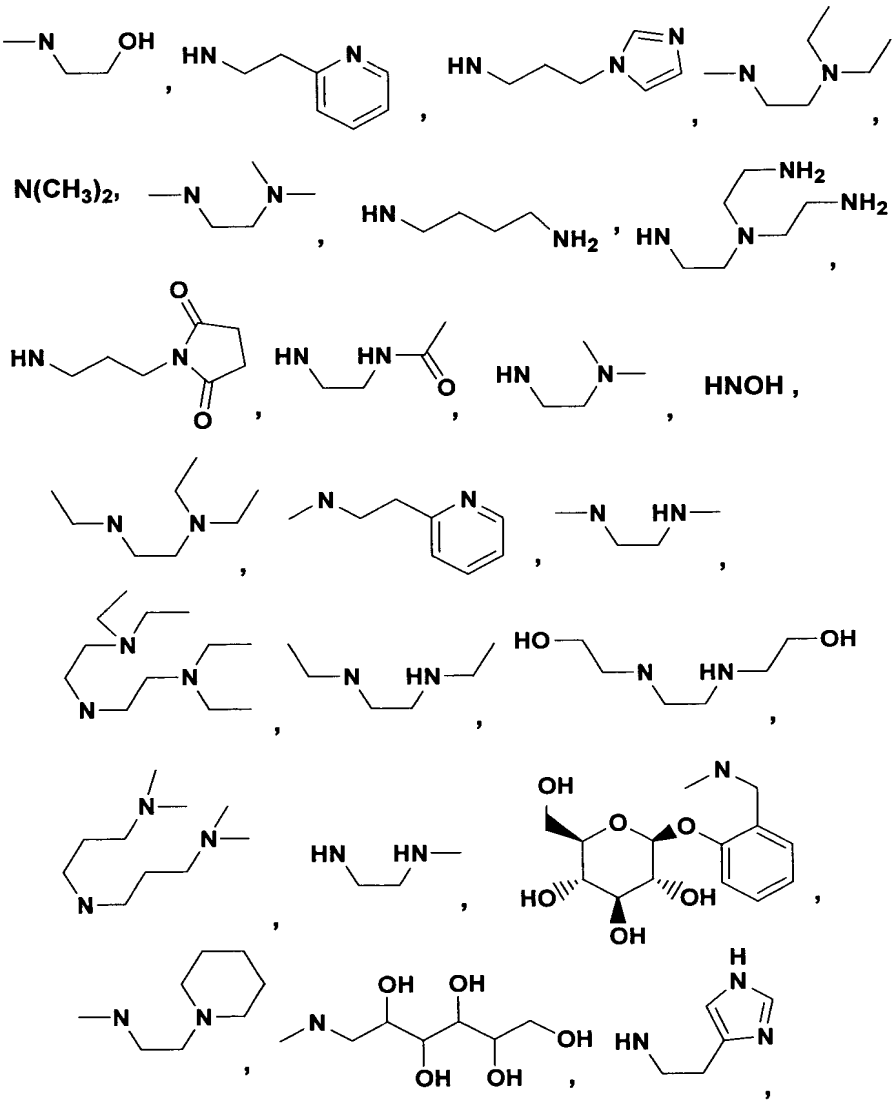


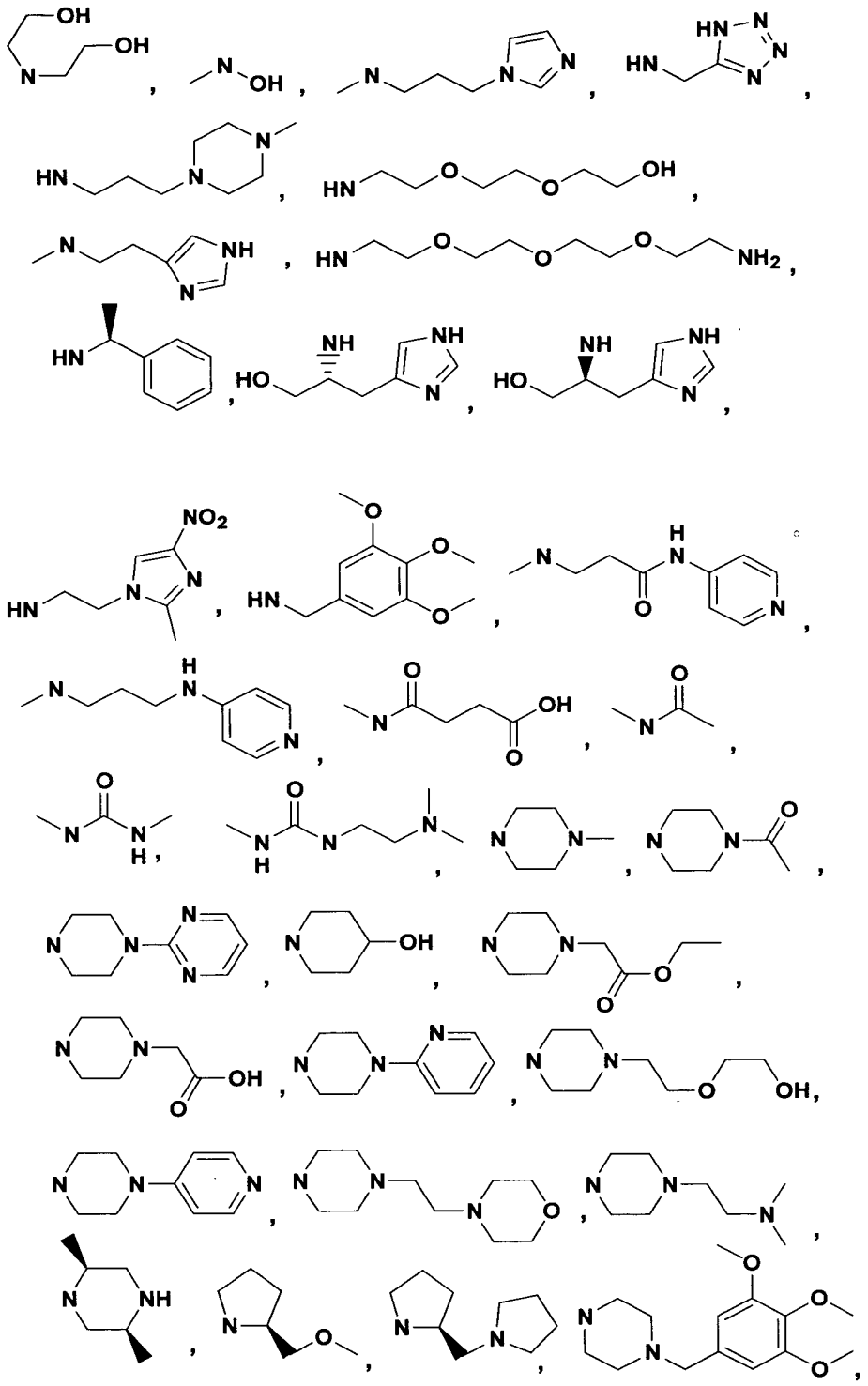
A fourth embodiment of a first aspect of the present invention is a compound of the third embodiment, including pharmaceutically acceptable salts thereof, wherein Y is NR.

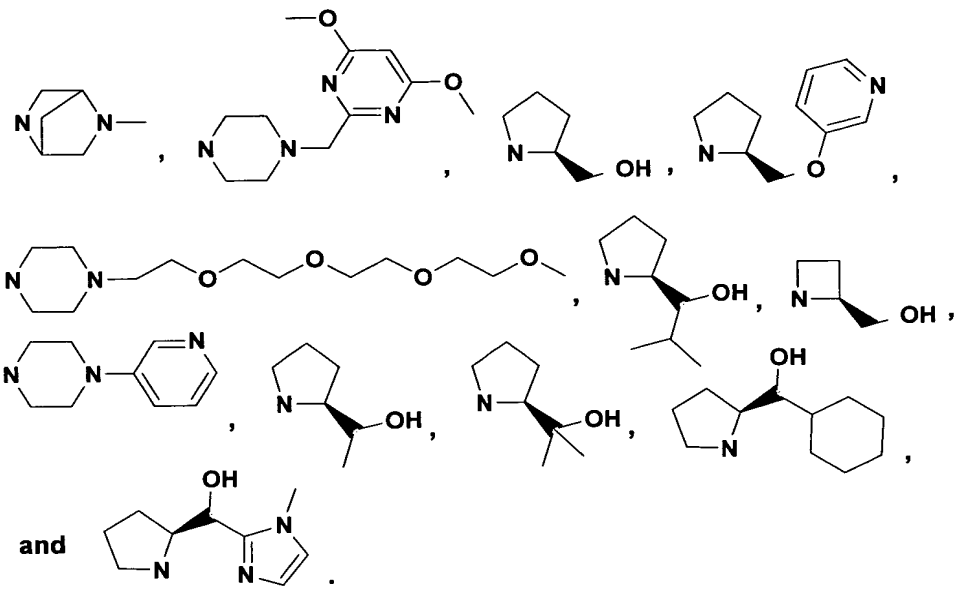
A fifth embodiment of a first aspect of the present invention is a compound of the fourth embodiment, including pharmaceutically acceptable salts thereof, wherein R is selected from the group consisting

of hydrogen, hydroxy, $-C(O)CH_3$, $-C(O)(CH_2)_2CO_2H$, $-C(O)NHCH_3$ and C_{1-4}alkyl, in which said C_{1-4}alkyl is optionally substituted with one hydroxy or di(C_{1-4}alkyl)amino.

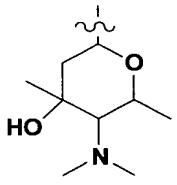
A sixth embodiment of a first aspect of the present invention is a compound of the fourth embodiment, including pharmaceutically acceptable salts thereof, wherein NRR^1 is selected from the group consisting of:







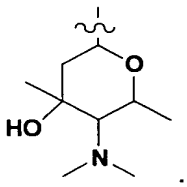
A seventh embodiment of a first aspect of the present invention is a compound of the sixth embodiment, including pharmaceutically acceptable salts thereof, wherein W is

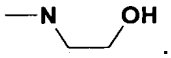


; R^2 is hydroxy; and R^3 is hydrogen.

An eighth embodiment of the present invention is a compound of the sixth embodiment, including pharmaceutically acceptable salts thereof, wherein R^2 and R^3 are each hydrogen.

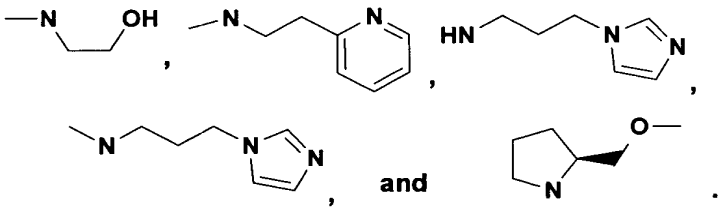
A ninth embodiment of a first aspect of the present invention is a compound of the eighth embodiment, including pharmaceutically acceptable salts thereof, wherein W is



A tenth embodiment of a first aspect of the present invention is the compound of the ninth embodiment, including pharmaceutically acceptable salts thereof, wherein NRR^1 is  .

An eleventh embodiment of a first aspect of the present invention is a compound of the sixth embodiment, including pharmaceutically acceptable salts thereof, wherein W is hydrogen;R^2 is hydroxy; and R^3 is hydrogen.

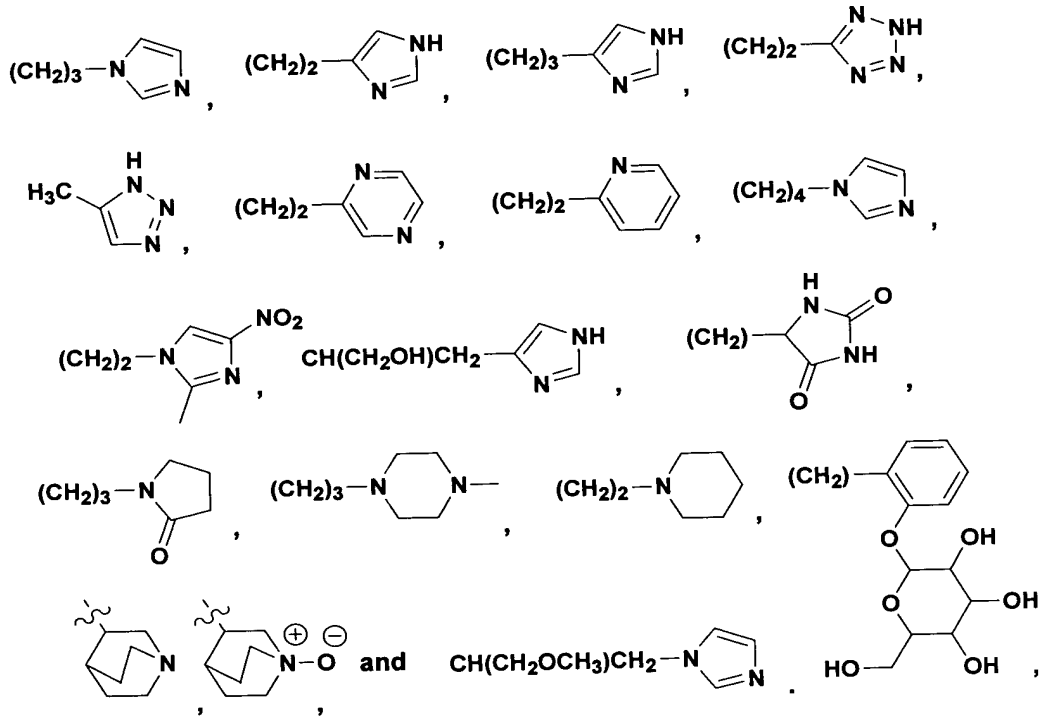
A twelth embodiment of a first aspect of the present invention is a compound of the eleventh embodiment, including pharmaceutically acceptable salts thereof, wherein NRR^1 is selected from the group consisting of:



A thirteenth embodiment of a first aspect of the present invention is a compound of the third embodiment, including pharmaceutically acceptable salts thereof, wherein Y is $S(O)_m$ in which m is 0 or 2;

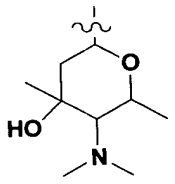
R^1 is selected from the group consisting of CH_3, CH_2CH_3, $(CH_2)_2OH$, $CH(CH_3)CH_2OH$, $CH_2[CH(OH)]_4CH_2OH$, $[(CH_2)_2O]_2(CH_2)_2OH$, $[(CH_2)_2O]_2(CH_2)_2OCH_3$, $[(CH_2)_2O]_2(CH_2)_2NH_2$, $[(CH_2)_2O]_2(CH_2)_2N(CH_3)_2$,

CH_2CO_2H, $(CH_2)_2CO_2H$, $CH(CO_2H)CH_2CO_2H$, $CH_2CH(NHC(O)CH_3)CO_2H$, $(CH_2)_2SO_3H$, $(CH_2)_4NH_2$, $(CH_2)_2N(CH_3)_2$, $(CH_2)_3N(CH_3)_2$, $(CH_2)_2N(CH_2CH_3)_2$, $(CH_2)_2NH(CH_3)$, $(CH_2)_2NH(CH_2CH_3)$, $(CH_2)_2NH(CH_2)_2OH$, $(CH_2)_2N[(CH_2)_2NH_2)]_2$, $(CH_2)_2NHC(O)CH_3$,

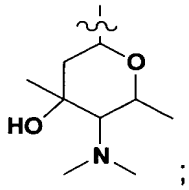


A fourteenth embodiment of a first aspect of the present invention is a compound of the thirteenth embodiment, including pharmaceutically acceptable salts thereof, wherein m is 0; and

W is hydrogen or



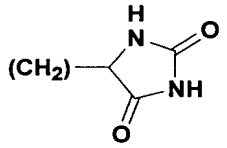
A fifteenth embodiment of a first aspect of the present invention is a compound of the fourteenth embodiment, including pharmaceutically acceptable salts thereof, wherein W is



;

R^2 is hydroxy; and R^3 is hydrogen.

A sixteenth embodiment of a first aspect of the present invention is a compound of the fifteenth embodiment, including pharmaceutically acceptable salts thereof, whereinR^1 is selected from the group consisting of CH_2CO_2H, $(CH_2)_2CO_2H$, $CH(CO_2H)CH_2CO_2H$, $CH_2CH(NHC(O)CH_3)CO_2H$, $(CH_2)_2SO_3H$, $(CH_2)_2N(CH_3)_2$,$(CH_2)_2N(CH_2CH_3)_2$,



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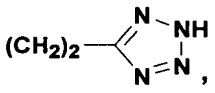

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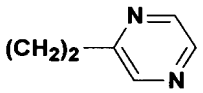

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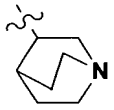

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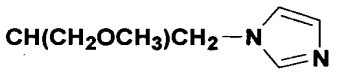
and



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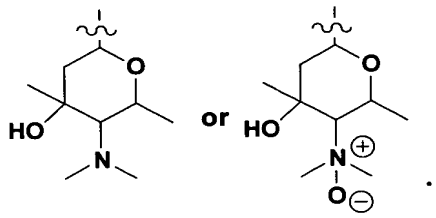
A seventeenth embodiment of a first aspect of the present invention is a compound of the fourteenth embodiment, including pharmaceutically acceptable salts thereof, wherein W is hydrogen;R^2 is hydroxy; and R^3 is hydrogen.

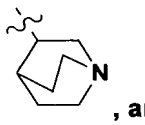
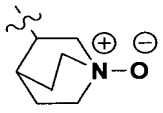
An eighteenth embodiment of a first aspect of the present invention is a compound of the seventeenth embodiment, including pharmaceutically acceptable salts thereof, wherein R^1 is CH_2CO_2H or $(CH_2)_2N(CH_2CH_3)_2$.

A nineteenth embodiment of a first aspect of the present invention is a compound of the thirteenth embodiment, including pharmaceutically acceptable salts thereof, wherein m is 2; and W is

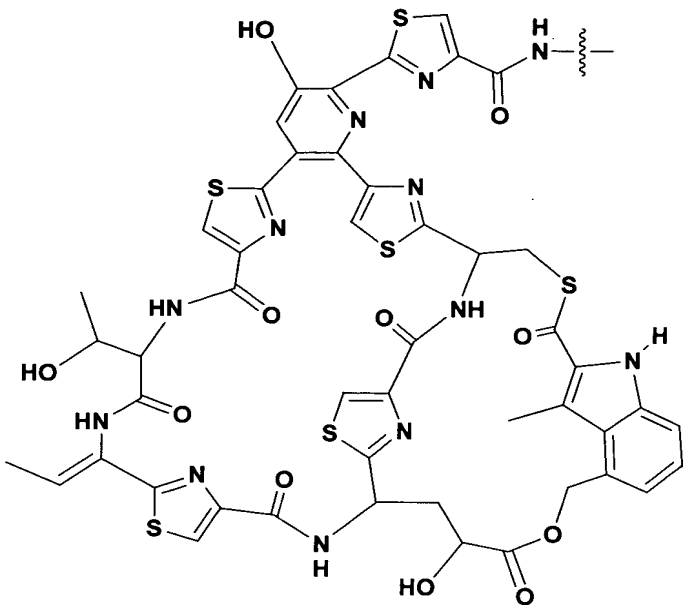


A twentieth embodiment of a first aspect of the present invention is a compound of the nineteenth embodiment, including pharmaceutically acceptable salts thereof, wherein R^2 is hydroxy; and R^3 is hydrogen.

A twentyfirst embodiment of a first aspect of the present invention is a compound of the twentieth embodiment, including pharmaceutically acceptable salts thereof, wherein R^1 is selected from the group consisting of:

$(CH_2)_2N(CH_2CH_3)_2$,  , and  .

A twentysecond embodiment of a first aspect of the present invention is a compound of the first embodiment, including pharmaceutically acceptable salts thereof, wherein Q is



A twentythird embodiment of a first aspect of the present invention is a compound of the twentysecond embodiment, including pharmaceutically acceptable salts thereof, wherein Y is NR.

A twentyfourth embodiment of a first aspect of the present invention is the compound of the twentythird embodiment, including pharmaceutically acceptable salts thereof, wherein R is methyl; and R^1 is 3-(imidazol-1-yl)-propyl.

A twentyfifth embodiment of a first aspect of the present invention is a compound of the twentysecond embodiment, including pharmaceutically acceptable salts thereof, wherein Y is S.

A twentysixth embodiment of a first aspect of the present invention is the compound of the twentyfifth embodiment, including pharmaceutically acceptable salts thereof, wherein R^1 is $(CH_2)_2N(CH_2CH_3)_2$.

A first embodiment of a second aspect of the present invention is a pharmaceutical composition which comprises a therapeutically effective amount of a compound as described in any of the embodiments of the first aspect, and a pharmaceutically acceptable carrier, adjuvant or diluent.

A first embodiment of a third aspect of the present invention is a method of treating or preventing bacterial or mycobacterial infection by administering to a mammal in need thereof a therapeutically effective amount of a compound as described in any of the embodiments of the first aspect.

A second embodiment of the third aspect of the present invention is the method of the first embodiment, wherein said bacterial infection is caused by a gram positive bacteria or a mycobacterium.

A third embodiment of a third aspect of the present invention is the method of the second embodiment, wherein said gram positive bacterial infection or mycobacterial infection is caused by methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus faecalis*, vancomycin-resistant *Enterococcus faecium* or *Mycobacteria tuberculosis*.

An "aryl" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted as specified.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of

nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, and pyrazinyl. The heteroaryl group may be substituted or unsubstituted as specified.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidinyl, piperazinyl, imidazolinyl, thiazolidinyl, pyrrolidinyl, aziridinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. The heteroalicyclic group may be substituted or unsubstituted as specified.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). For example, the term "C_{1-6} alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like. More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. The alkyl group may be substituted or unsubstituted as specified. When substituted, the substituent group(s) may include, for example, one or more individually selected from aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, amino, etc.

A "cycloalkyl" group refers to an all-carbon monocyclic or bicyclic ring system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane and adamantane.

A "hydroxy" group refers to an –OH group.

An "alkoxy" group refers to an –O-alkyl group as defined herein.

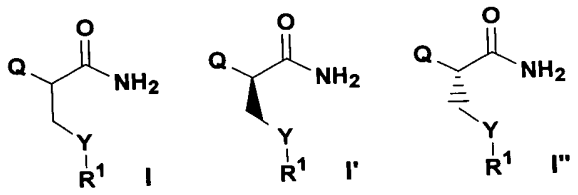
An "amino" group refers to an $-NH_2$ group. One or both of the hydrogens attached to the amino nitrogen can be replaced by alkyl goups to provide an alkylamino or di(alkyl)amino group, respectively.

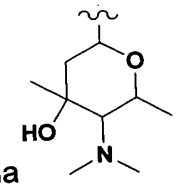
It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding.

Physiologically acceptable salts of compounds disclosed herein are within the scope of this invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, and without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or

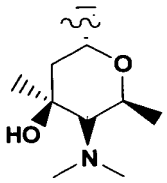
potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)-aminomethane), or with bases such as piperidine or morpholine.

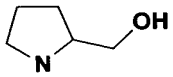
The compounds of Formula I may exist as single diastereomers or as mixtures thereof. The general formula I is intended to encompass single diastereomers such as those depicted below as I' and I" and any mixtures thereof. Single diastereomers may be obtained from diastereomeric mixtures by methods such as preparative HPLC as described hereinafter.



The compounds of the present invention may have chiral centers other than those centers whose stereochemistry is depicted in Formula I, and therefore may occur as mixtures of diastereomers or as single diastereomers. It is understood that all such isomeric forms, and any mixtures thereof, are included in the present invention. For example, when the group W in a compound of Formula I is a sugar residue of the formula 

it is to be understood to encompass racemic forms of the sugar residue as well as chiral forms of the sugar residue such as



. As an additional example, in a compound of Formula I when Y is NR, the moiety NRR^1 could be a group such as 2-hydroxymethyl pyrrolidinyl,  . It is to be understood that the 2-hydroxymethyl pyrrolidinyl group shown encompasses both racemic as well as chiral forms of the 2-hydroxymethyl pyrrolidinyl group. In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are within the scope of this invention.

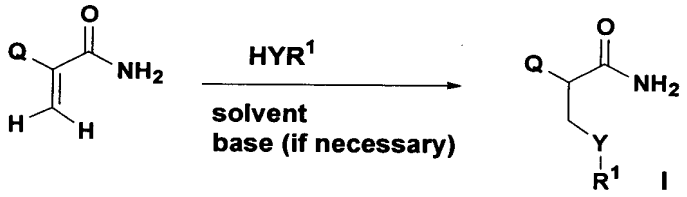
The following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, are used throughout the description of the invention and examples. Some of the abbreviations used are as follows:

h	=	hour(s)
rt	=	room temperature
mol	=	mole(s)
mmol	=	millimole(s)
g	=	gram(s)
mg	=	milligram(s)
CH_2Cl_2	=	Dichloromethane
DMF	=	N, N-Dimethylformamide
DMSO	=	Dimethylsulfoxide
Et_3N	=	Triethylamine
HCl	=	Hydrochloric Acid
MCPBA	=	3-Chloroperoxybenzoic acid
NMP	=	1-Methyl-2-pyrrolidinone
THF	=	Tetrahydrofuran

TFA = Trifluoroacetic acid

The general procedures used to synthesize the novel thiazolyl peptide compounds within Formula I are depicted in Reaction Schemes 1-4, below. Reaction Scheme 1 shows the preparation of compounds of Formula I by the Michael type addition of an appropriate nucleophile, HYR^1, to an appropriately substituted and activated carbon-carbon double bond of a thiazolyl peptide antibiotic such as a nocathiacin or nosiheptide.

Reaction Scheme 1

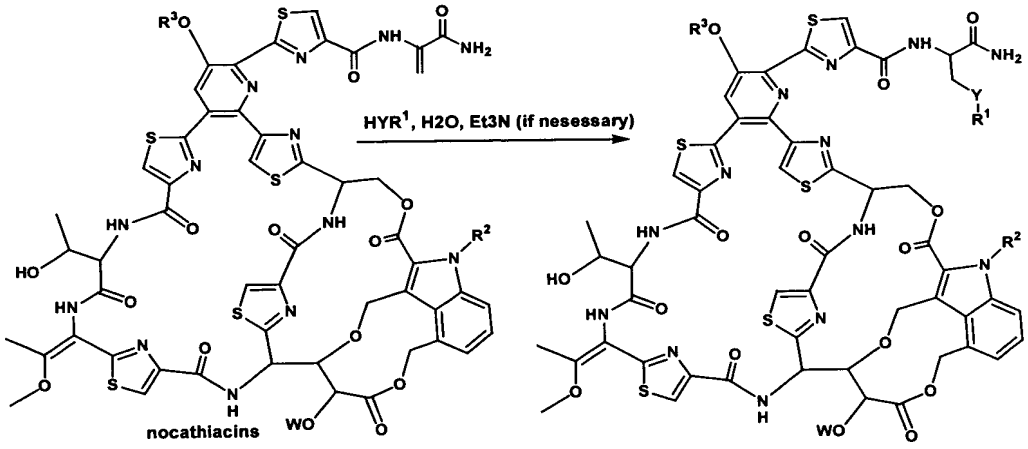


I

The reaction is typically run in a polar solvent and may require the presence of an organic base. Appropriate nucleophiles of formula HYR^1 include primary amines, secondary amines and thiols. Thiazolyl peptide antibiotics which may be employed as starting materials for the preparation of compounds of Formula I, include any thiazolyl peptide antibiotic which contains a carbon-carbon double bond which can act as a Michael acceptor for the Michael donor, HYR^1. Thiazolyl peptide antibiotics, including, but not limited to, nocathiacins, nosiheptide, thiostrepton, thiopeptin Ba, siomycins, micrococcin, SCH 40832, S-54832, and GE-37468 may be appropriate starting materials for the Michael type additions described herein. The thiazolyl peptide nocathiacins and nosiheptide serve as precursors to compounds of Formula I. It is also understood that certain thiazolyl peptide antibiotics contain more than one carbon-carbon double bond which can act as a Michael acceptor. In such cases, it is understood that between one and all of the thiazolyl peptide Michael acceptor carbon-carbon double bonds can react with the nucleophile, HYR^1, to provide compounds in a similar fashion to those of

Formula I. The synthesis of the compounds of Formula I is typically carried out in a polar solvent including, but not limited to, water, DMF, DMSO, dioxane, THF, CH_2Cl_2, NMP, methanol, ethanol, propanol, butanol and any mixtures thereof. A preferred solvent for reactions which employ nocathiacins as the starting material is water. Reactions which employ nosiheptide or thiostrepton as starting materials are preferably carried out in a mixture of DMF and water. Certain reactions require the addition of an organic base, such as triethylamine, *N,N*-diisopropylethylamine, 4-methylmorpholine, 1, 8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1, 5-Diazabicyclo[4.3.0]non-5-ene (DBN), 1, 4-Diazabicyclo[2.2.2]octane (Dabco) or pyridine. Triethylamine is a preferred base, when a base is required. The Michael addition reactions, as shown in Reaction Scheme 1, may be carried out within a temperature range of –50 °C to 50 °C. A preferred method is to initiate the reaction at room temperature and then maintain the reaction mixture within the temperature range of –20 °C to 0 °C for a period of 3 to 24 hours. It is understood by one skilled in the art that certain reactions, such as reactions employing sterically hindered nucleophiles, may require extended reaction times outside the typical period of 3 to 24 hours.

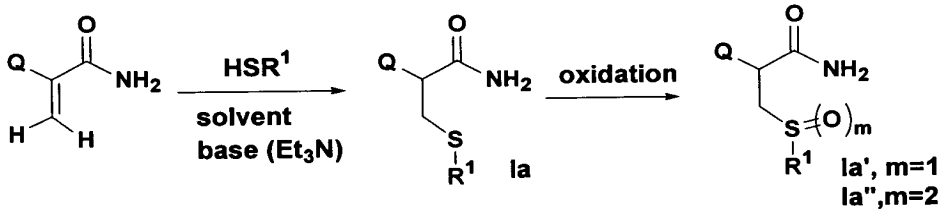
Reaction Scheme 1A



Reaction Scheme 1A depicts the preparation of a nocathiacin derivative within Formula I. The nocathiacin starting material is treated with an appropriate amine or thiol of general formula HYR^1 in water and in the presence of a tertiary amine base, such as triethylamine, if necessary.

Reaction Scheme 2 depicts the preparation of compounds of Formula Ia, Ia' and Ia" wherein the Michael donor (i.e. nucleophile) employed is a thiol. The presence of an organic base, preferably triethylamine, is required when a thiol of general formula R^1-SH is used as the Michael donor. The sulfide compounds of Formula Ia which are formed as shown in the first step of Scheme 2 can then be oxidized to provide sulfoxide (m = 1) of Formula Ia' and sulfone (m = 2) of Formula Ia"

Reaction Scheme 2

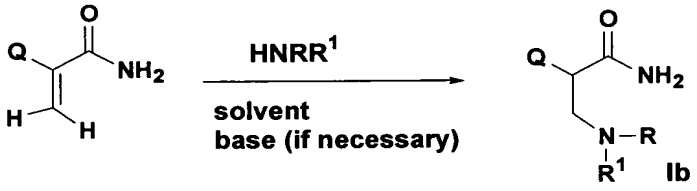


derivatives as shown in the second step of Scheme 2. Oxidation of the sulfide to the corresponding sulfoxide (m = 1) may be accomplished by treatment with mCPBA in the presence of either TFA or sodium bicarbonate as described by J.C. Barriere and J.M. Paris, 'From the Michael Reaction to the Clinic.' In: Anti-infectives: Recent Advances in Chemistry and Structure-Activity Relationships. Bentley, P.H., O'Hanlon, P.J. eds, The Royal Society of Chemistry, Cambridge, 1997, Chpt. 3, p 36. Oxidation of the sulfide to the sulfone (m = 2), shown in Scheme 2, may be accomplished by methods as described at p 37-38 of the preceding reference and further described in Chaterjee, D.; Harris, N.V.; Parker, T; Smith, C.; Warren, J.P. Eur. Patent Appl. 252,720 (use of sodium periodate and ruthenium trichloride) and Radisson, X; World

Patent WO 92/ 01692-A, 1992 (use of hydrogen peroxide with sodium tungstate).

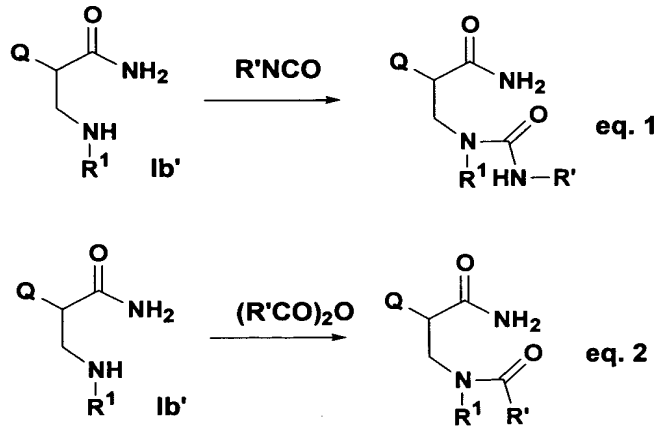
Reaction Scheme 3 depicts the preparation of compounds of Formula Ib wherein the Michael donor employed is a primary or secondary amine of the general formula $HNRR^1$. The presence of an organic base, preferably triethylamine, may be required when certain amines are used.

Reaction Scheme 3



Reaction Scheme 4, below, depicts further derivatization of compounds of Formula I which possess a reactive amine residue. The amine residue can react with isocyanates, such as methyl isocyanate, of general formula R'NCO (wherein R' typically represents a C_{1-6}alkyl) to provide urea derivatives as shown in equation 1 of Scheme 4. Alternatively, reaction with anhydrides of general formula $(R'CO)_2O$ (wherein R' typically represents a C_{1-6}alkyl or both R' groups taken together represent a C_{2-4}alkylene) provides amide derivatives as shown in equation 2 of Scheme 4. Useful anhydrides include, but are not limited to, acetic anhydride and succinic anhydride.

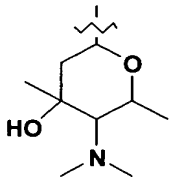
Reaction Scheme 4



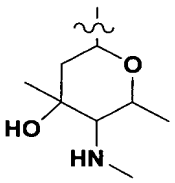
STARTING MATERIALS

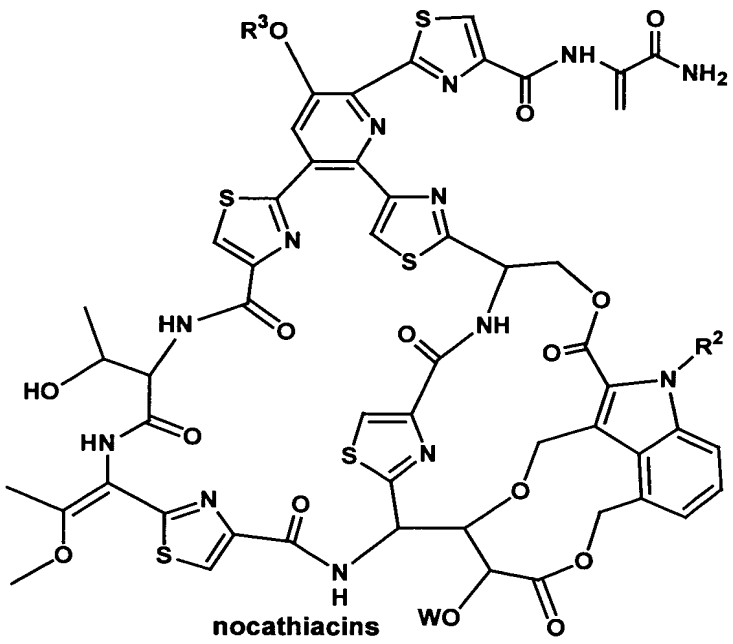
The nocathiacin antibiotics and nosiheptide may be employed as starting materials for the synthesis of compounds of Formula I. The other thiazolyl peptide antibiotics disclosed may undergo the Michael type addition of a nucleophile of the general formula HYR^1 in an analogous fashion.

The nocathiacin starting materials were prepared by fermentation using microorganism ATCC-202099 and subsequent isolation as described by J. E. Leet *et al.* in PCT Appl. WO 00/03722 (published 1/27/2000); and PCT Appl. WO 00/14100 and also by Sasaki, T. *et al.* in *J. of Antibiotics* **1998**, *51*, No. 8, pp. 715-721. The preparation of nocathiacin I and III (see structure below) is described more fully in commonly-owned US 6,218,398 (issued 4/17/2001) which is hereby incorporated by reference in its entirety. The groups W, X, R^3 and R^4 are as defined in the specification. For nocathiacin I (see general structure below), R^2 is OH, R^3 is H, and W is



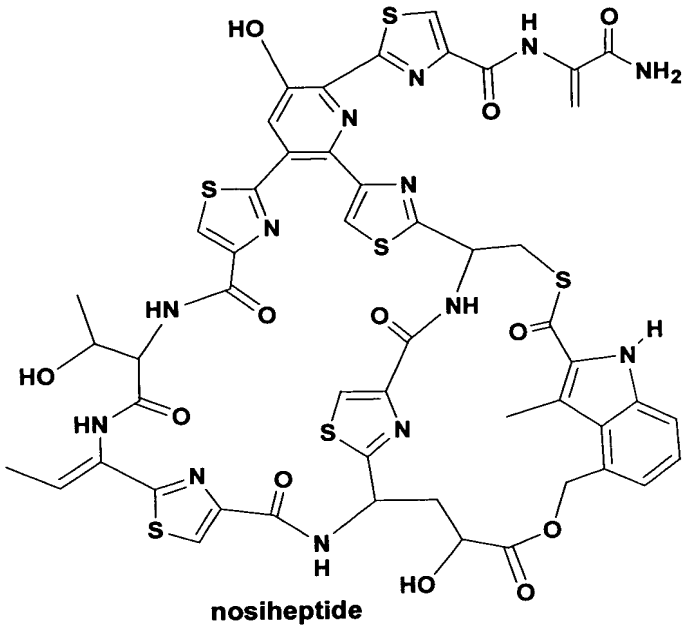
whereas for nocathiacin III, R^2 is OH; W and R^3 are H. For the nocathiacin derivative designated MJ347-81F4-B, the preparation of which is described by Sasaki, T. *et al.* in *J. of Antibiotics* **1998**, *51*, No. 8, pp. 715-721, R^2 is OH, R^4 is H, and W is





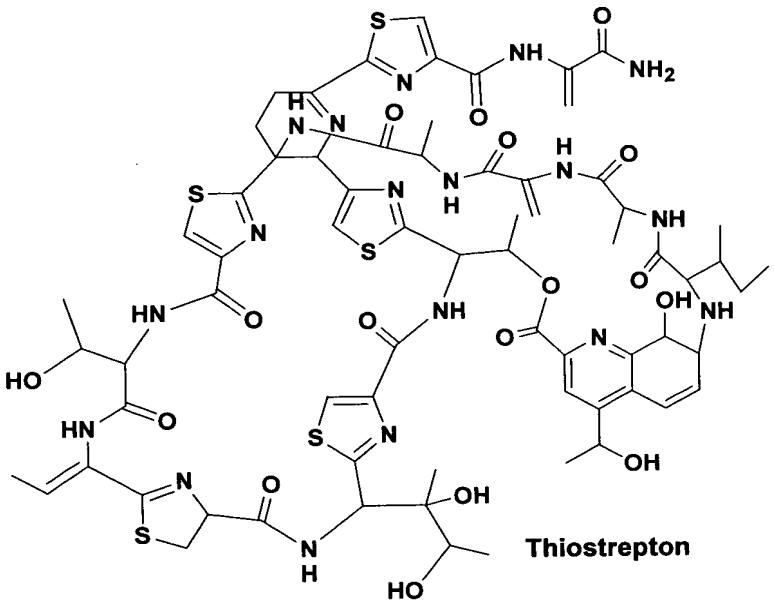
nocathiacins

Nosiheptide can be prepared and isolated according to methods described in Pascard, C. *et al.* in *J. Am. Chem. Soc.* **1977**, *99*, 6418-6423 and Benazet, F. *et al.* in *Experientia* **1980**, *36*, 414-416.



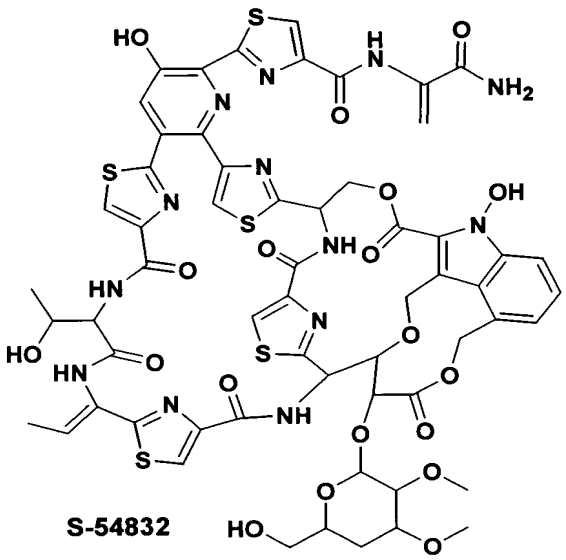
nosiheptide

Thiostrepton is a fermentation product which is produced and isolated from *Streptomyces azureus* as described by Vandeputte, J.; and Dutcher, J.D. in *Antibiotics Ann.* **1956**, 560 and also in Pagano, J.F. et al. *Antibiotics Ann.* **1955-1956**, 554-559.



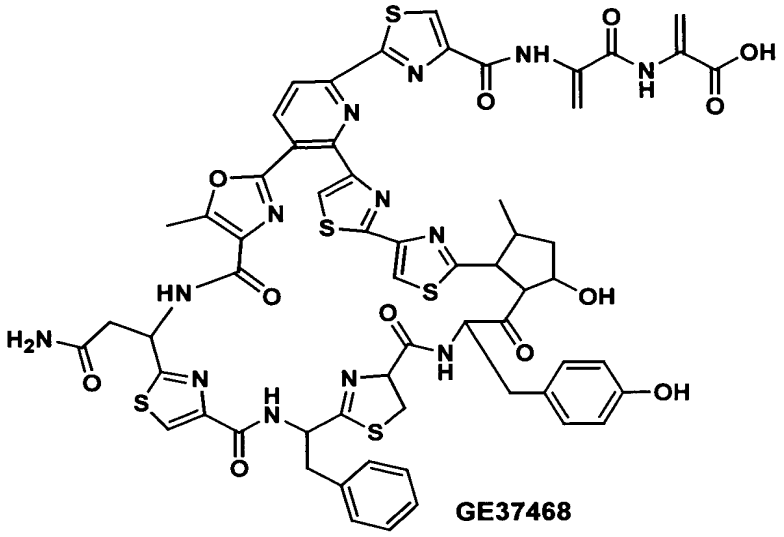
Thiostrepton

Antibiotic S 54832 is produced by fermentation using a *Micromonospora globosa* strain and isolated according to the methods described by Keller-Juslen, C.; Kuhn, M.; and King, H.D. in U.S. Patent 4,478,831 (1984).



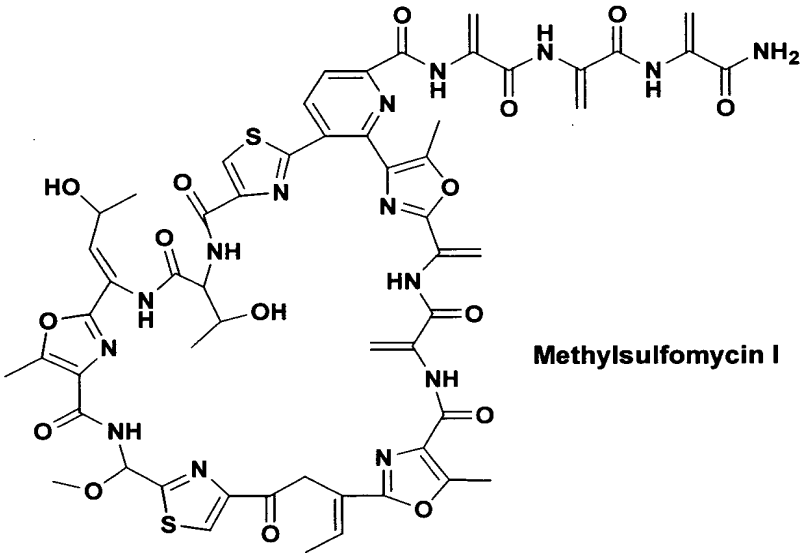
S-54832

Antibiotic GE37468 (shown below) may be produced by fermentation using *Streptomyces* sp. Strain ATCC 55365 and isolated according to procedures disclosed by Stella, S. *et al* in *J. of Antibiotics* **1995**, *48*, No. 8, 780-786.



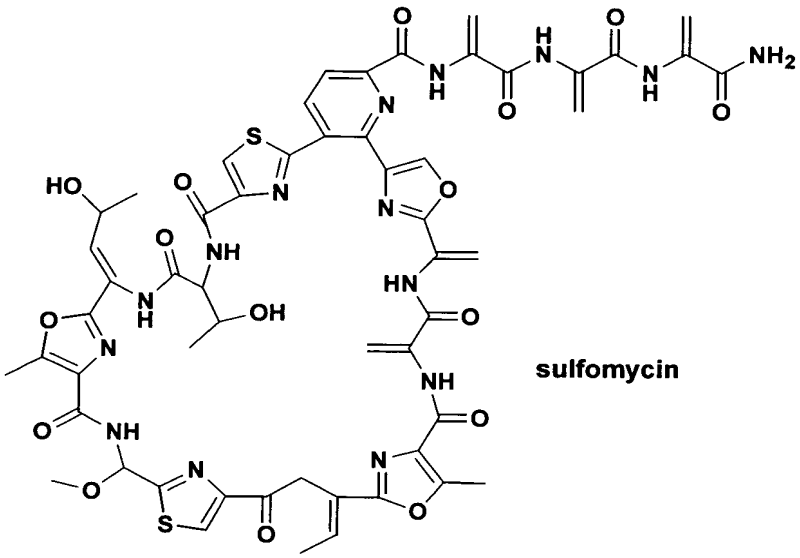
GE37468

Methylsulfomycin I is produced by fermentation using *Streptomyces* sp. HIL Y-9420704 according to procedures disclosed by Kumar *et al.* in *J. Nat. Prod.* **1999**, *62(11)*, 1562-1564.



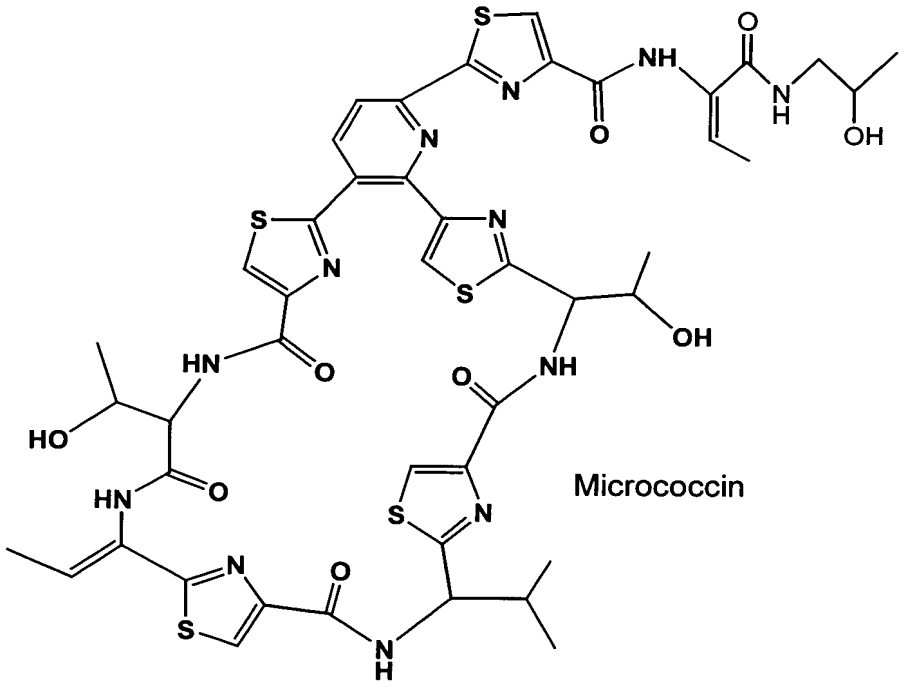
Methylsulfomycin I

Sulfomycin can be prepared by fermentation and isolated as described within *J. Am. Chem. Soc.* **1996**, *118*, 11363.



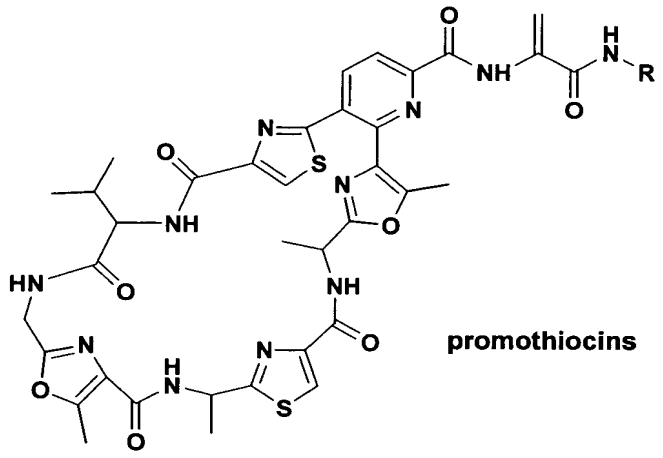
sulfomycin

Micrococcin can also be obtained by fermentation and isolated as described in *Antibiotics* **1975**, *3*, 480.



Micrococcin

Promothiocin A (wherein R = H) and Promothiocin B (wherein R = $C(=CH_2)CONHC(=CH_2)CONH_2$) can be prepared by fermentation according to



promothiocins

the methods described by Yun, B.S. et al. in *J. Antibiotics* **1994**, *47*, 510-514 or by total synthesis according to the methods described by Bagley, B.C. et al. in *J. Am. Chem. Soc.* **2000**, *122*, 3301-3313.

SYNTHESIS

The synthesis of the compounds of Formula I was carried out by standard methods practiced by one skilled in the art. Purification of the compounds of Formula I by medium pressure liquid chromatography (MPLC) was performed using Waters Preparative C-18 reverse phase material, 125 Å, 55-105 μm which was packed in a Michel-Miller column. The mobile phase was pumped through the packed Michel-Miller column using an FMI Lab Pump (Model RP-SY, Fluid Metering Inc., Oyster Bay, NY) at system pressures generally within the range of 20-80 psi. Typical eluents used for MPLC include mixtures of acetonitrile and water or methanol and water with the pH of these eluents sometimes being adjusted to 4-5 by the addition of dilute aqueous HCl or TFA. The

compounds of the present invention could also be purified by standard reverse phase column chromatography using Waters Preparative C-18 reverse phase material, 125 Å, 55-105 μm and acetonitrile and water or methanol and water as eluents, with the pH of these eluents sometimes being adjusted to 4-5 by the addition of dilute aqueous HCl or TFA. Compounds purified by preparative HPLC were typically diluted in water, DMF, MeOH or some mixture thereof and purified on a Shimadzu LC-10A automated preparative HPLC system. A representative HPLC method useful for the purification of compounds of Formula I is given below.

General Preparative HPLC Method (i.e., compound purification)

Purification Method: Initial gradient (20% B, 80% A) ramp to final gradient (100% B, 0% A) over 20 minutes, hold for 3 minutes (100% B, 0% A)

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

Column: YMC C18 S5 20x100 mm column

Detector Wavelength: 220 nm

The compounds of Formula I purified by preparative HPLC were obtained as trifluoroacetic acid salts which could be converted to the corresponding hydrochloride salt using AG 1-X2 Resin, 100-200 mesh, chloride form, obtained from BioRad (Hercules, CA). The AG 1-X2 resin was placed in a fritted syringe and washed with water. An aqueous solution of a trifluoroacetic acid salt of a compound of Formula I was then filtered through the resin. The resin was then rinsed with three volumes of water. The combined aqueous fractions were frozen and lyophilized to

provide the compound of Formula I as a hydrochloride salt. NMR spectra were recorded on a Bruker DPX-500, DPX-300 or Varian XL-300. Chemical shifts (δ) are expressed in ppm. Coupling constants (J) are expressed in Hertz. Mass spectra (MS) for the compounds were obtained using Flow Injection Mass Spectrometry (electrospray ionization technique) on a Finnegan SSQ 7000 mass spectrometer. Liquid Chromatography/ Mass Spectrometry (LC/MS) was performed on a Hewlett-Packard 1100 liquid chromatograph coupled to a Finnegan LCQ mass spectrometer using an electrospray ionization technique. High Resolution Mass Spectrometry (HRMS) for the compounds was obtained using a Finnegan MAT 900 mass spectrometer with 5000 resolution at 10% valley.

General Procedure for the Michael Addition of Amines to a Thiazolyl Peptide Antibiotic:

To a stirred solution of an appropriate amine (10 equiv.) in an appropriate solvent, (C = 0.002 M) at room temperature was added an appropriate thiazolyl peptide antibiotic (1 equiv.). The reaction mixture was stirred for 3 to 5 minutes until the reaction mixture becomes a clear homogeneous solution. If the reaction mixture did not become a clear solution then enough Et_3N, (~ 2-4 equiv.) was added dropwise and stirred until the reaction mixture becomes a clear solution. The resulting reaction mixture was maintained at approximately -20 °C for a period of 3 to 24 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure or it was quenched by addition of TFA or HCl (1N) until the pH of the mixture was acidic and then concentrated under reduced pressure. The residue was then dissolved in a suitable solvent such as water, DMF, methanol or a mixture thereof and was purified using Prep-HPLC and/or MPLC on preparative C-18 column using methanol/water or acetonitrile water as eluent. The eluent may contain dilute HCl or TFA (such that the pH is 4-5). Alternatively, the reaction

mixture can be directly subjected to purification by HPLC or MPLC or quenched with HCl or TFA and purified by HPLC or MPLC. The fractions containing the desired product as a trifluoroacetic acid, or hydrochloride salt were combined and concentrated to approximately 50 mL and then freeze dried to give products as yellow fluffy solids.

General Procedure for the Michael Addition of Thiols to a Thiazolyl Peptide Antibiotic:

To a stirred suspension of an appropriate thiazolyl peptide antibiotic (0.20 mmol) in an appropriate solvent (10 mL) was added Et_3N (70 μL, 0.5 mmol) and continued stirring at room temperature for 3 to 5 minutes until the reaction mixture becomes a clear homogeneous solution. To this solution was added an appropriate thiol (5-10 equiv.) and, if needed, more Et_3N (usually 2-3 mmol) to bring the reaction mixture to a homogeneous solution. The reaction mixture was then maintained at –20 °C for a period of 3 to 24 h. The reaction mixture was then diluted with water, aqueous sodium bicarbonate or dilute hydrochloric acid and purified using Prep-HPLC or MPLC on preparative C-18 column using methanol/water or acetonitrile/water as eluent. The eluent may contain dilute HCl or TFA (such that the pH is 4-5). The fractions containing the desired product as a trifluoroacetic acid, triethylammonium, sodium or hydrochloride salt were combined and concentrated to approximately 50 mL and then freeze dried to give products as yellow fluffy solids.

When the compounds of Formula I are employed as pharmaceutical compositions for the treatment of bacterial infections, they may be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50%

of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be

advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

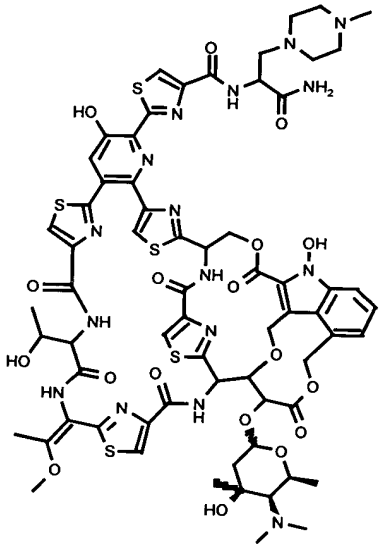
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

EXAMPLES

The following examples set out the preparation of the novel thiazolyl peptide derivatives and their biological properties. Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

COMPOUNDS OF FORMULA I

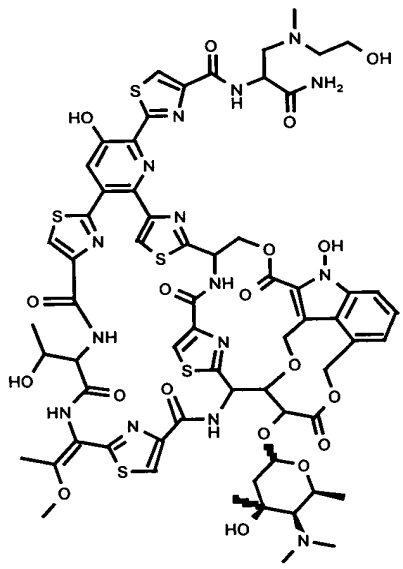
EXAMPLE 1



An example of the general procedure for the Michael addition of amines to a Nocathiacin: To a stirred solution of 1-methylpiperazine (0.38 mL, 3.50 mmol) (10 equiv.) in water (17.5 mL) at room temperature was added Nocathiacin I (0.5 g, 0.35 mmol) (1 equiv.). The reaction mixture was stirred for 3 to 5 minutes until it became a clear homogeneous solution. The reaction mixture was then maintained at –20 °C for 16 h. The reaction mixture was then quenched with 1N aqueous hydrochloric acid and subjected to medium pressure chromatography, as described above. The product containing fractions were concentrated under reduced pressure, frozen and lyophilized to afford the product as a yellow powder (0.223 g, 41% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.03 (bs, 1H), 10.79 (s, 1H), 10.18 (bs, 1H), 9.12 (s, 1H), 9.02 (m, 1H), 8.71 (m, 1H), 8.65 (s, 1H), 8.59 (d, J = 10.0 Hz, 1H), 8.54 (s, 1H), 8.51 (s, 1H), 8.23 (s, 1H), 8.03 (s, 1H), 7.89 (d, J = 5.0 Hz, 1H), 7.86 (d, J = 10.0 Hz, 1H), 7.74 (d, J = 10.0 Hz, 1H), 7.63 (s, 1H), 7.36 (m, 2H), 7.23 (s, 1H), 7.09 (d, J = 10.0 Hz, 1H), 6.02 (d, J = 10.0 Hz, 1H), 5.75 (m, 1H), 5.71 (d,

J = 10.0 Hz, 1H), 5.22 (d, J = 5.0 Hz, 1H), 5.05 (m, 3H), 4.79 (d, J = 10.0 Hz, 1H), 4.66 (m, 1H), 4.53 (d, J = 10.0 Hz, 1H), 4.30 (d, J = 10.0 Hz, 1H), 4.25 (m, 1H), 4.15 (d, J = 10.0 Hz, 1H), 4.05 (d, J = 10.0 Hz, 1H), 3.19 (m, 4H), 3.45-3.25 (m, 6H), 3.12-2.80 (m, 7H), 2.73 (m, 2H), 2.54 (s, 2H), 2.12 (m, 1H), 2.00 (s, 3H), 1.93 (d, J = 15.0 Hz, 1H), 1.60 (s, 3H), 1.16 (m, 3H), 0.80 (d, J = 10.1 Hz, 3H). MS: 1538.1 $(M+H)^+$, 1535.5 $(M-H)^-$; HRMS (ES) calcd. for $C_{66}H_{73}N_{16}O_{18}S_5$ $(M+H)^+$: 1537.389, found: 1537.386. Anal. Calcd. for $C_{66}H_{72}N_{16}O_{18}S_5 \cdot 2HCl \cdot 6H_2O$: C, 46.12; H, 5.04; N, 13.04; S, 9.33; Cl, 4.13. Found: C, 46.33; H, 4.98; N, 12.82; S, 9.55; Cl, 4.04.

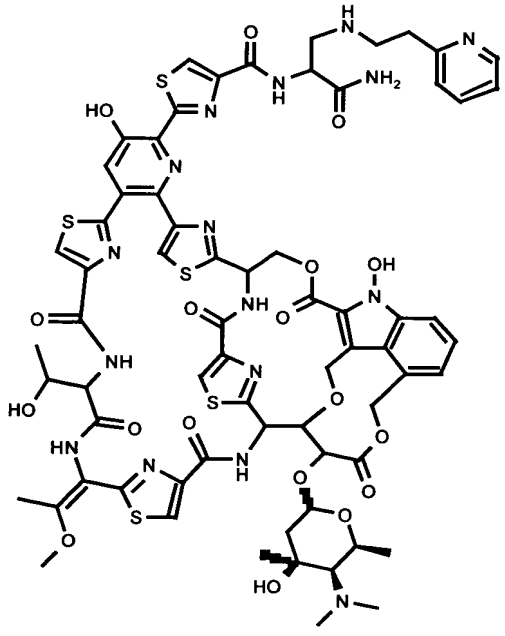
EXAMPLE 2



Following the procedure as described in Example 1 using Nocathiacin I (0.5 g, 0.35 mmol) and 2-(methylamino)ethanol (0.28 mL, 3.50 mmol) in water (17.5 mL). The reaction mixture was then quenched with 1N aqueous hydrochloric acid and subjected to medium pressure chromatography. The product containing fractions were concentrated under reduced pressure, frozen and lyophilized to afford the product as a

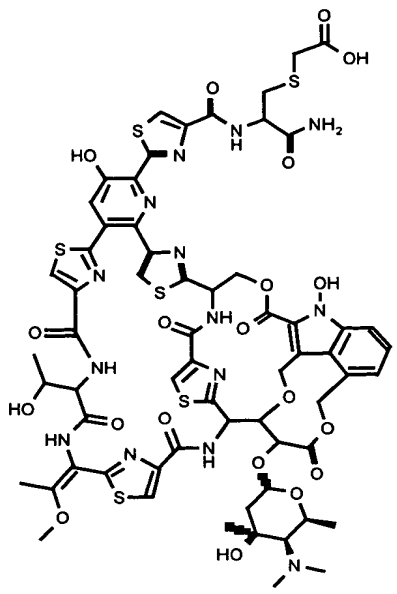
yellow powder (0.30g, 57% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.95 (dd, J = 8.33, J = 17.50, 1H), 10.78 (s, 1H), 9.60-9.35 (m, 2H), 9.12 (s, 1H), 8.75 (bs, 1H), 8.66 (s, 1H), 8.59 (s, 2H), 8.54 (s, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.93 (d, J = 18.2Hz, 1H), 7.85 (m, 2H), 7.81 (d, J = 9.9Hz, 1H), 7.54 (d, J = 18.0 Hz, 1H), 7.35 (m, 2H), 7.19 (d, J = 9.8 Hz, 1H), 6.40 (s, 1H), 6.03 (d, J = 15.0 Hz, 1H), 5.75 (m, 1H), 5.71 (d, J = 14.9 Hz, 1H), 5.33 (bs, 1H), 5.21 (d, J = 20.0 Hz, 1H), 5.05 (m, 3H), 5.00 (m, 1H), 4.72 (d, J = 14.7 Hz, 1H), 4.52 (d, J = 14.8 Hz, 1H), 4.30 (d, J = 10.1 Hz, 1H), 4.25 (m, 1H), 4.15 (d, J = 9.8 Hz, 1H), 4.05 (d, J = 10.0 Hz, 1H), 3.94-3.85 (m, 4H), 3.77 (m, 2H), 3.72-3.61 (m, 2H), 3.39 (m, 4H), 3.17, (s, 4H), 3.12 (s, 1H), 2.89 (m, 1H), 2.73 (s, 2H), 2.54 (m, 1H), 2.13, (m, 1H), 2.00 (s, 3H), 1.93 (d, J = 9.9 Hz, 1H), 1.61 (s, 3H), 1.15 (s, 3H), 0.80 (d, J = 6.9 Hz, 3H). MS: 1512.4 $(M+H)^+$, 1511.6 $(M-H)^-$; HRMS (ES) calcd. for $C_{64}H_{70}N_{15}O_{19}S_5$ (M+1): 1512.358, found: 1512.358. Anal. Calcd. for $C_{64}H_{69}N_{15}O_{19}S_5 \cdot 2HCl \cdot 4H_2O$: C, 46.37; H, 4.80; N, 12.67; S, 9.67; Cl, 4.28. Found: C, 46.45; H, 4.76; N, 12.77; S, 9.84; Cl, 4.69.

EXAMPLE 3



Following the procedure described in Example 1 using Nocathiacin I (0.5 g, 0.35 mmol) and 2-(2-aminoethyl)pyridine (0.42 mL, 3.50 mmol) in water (17.5 mL) afforded the product as a yellow powder (0.25g, 46% yield). ^{1}H NMR (500 MH z, MeOD): δ 10.73 (bs, 1H), 9.29 (bs, 1H), 9.12 (s, 1H), 8.66 (s, 1H), 8.60 (d, J = 8.0 Hz, 1H), 8.55 (s, 1H), 8.52 (s, 1H), 8.42 (t, 1H), 8.27 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.88 (d, J = 11.1 Hz, 1H), 7.73 (m, 3H), 7.48 (m, 1H), 7.34 (m, 3H), 7.23 (m, 1H), 7.18 (d, J = 7.0 Hz, 1H), 6.00 (d, J = 12.1 Hz, 1H), 5.74 (m, 1H), 5.68 (d, J = 9.6 Hz, 1H), 5.22 (m, 1H), 5.07 (m, 2H), 4.94 (d, J = 4.4 Hz, 1H), 4.85 (m, 1H), 4.76 (d, J = 10.3 Hz, 1H), 4.50 (d, 11.1, 1H), 4.31 (d, J = 9.7 Hz, 1H), 4.26 (t, J = 5.20 Hz, 1H), 4.10 (d, J = 10.5 Hz, 1H), 4.04 (d, J = 11.1 Hz, 1H), 3.91 (s, 3H), 3.76 (m, 1H), 3.60-3.23 (m, 12H), 3.09 (bs, 2H), 2.60-2.38 (m, 5H), 2.09 (m, 1H), 1.99 (s, 2H), 1.96 (m, 1H), 1.80 (d, J = 14.0 Hz, 1H), 1.43 (s, 3H), 1.25-1.09 (m, 3H), 0.57 (d, J = 6.0 Hz, 3H). MS: 1559.7 $(M+H)^+$, 1558.5 (M^-); HRMS (ES) calcd. for $C_{68}H_{71}N_{16}O_{18}S_5(M+H)^+$: 1559.374, found: 1559.374. Anal. Calcd. for $C_{68}H_{70}N_{16}O_{18}S_5 \cdot 2HCl \cdot 3H_2O$: C, 48.42; H, 4.66; N, 13.29; S, 9.50; Cl, 4.28. Found: C, 48.40; H, 4.63; N, 13.18; S, 9.36; Cl, 4.28.

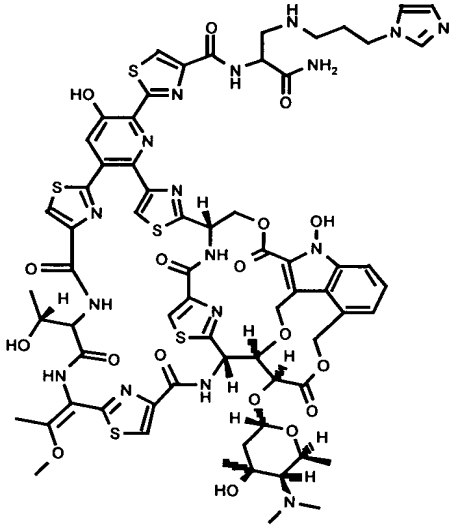
EXAMPLE 4



To a stirred suspension of Nocathiacin I (287.5 mg, 0.2 mmol) in water (10 mL) was added triethylamine (0.35 mL, 2.5 mmol). The mixture was stirred until it became a clear yellow solution. To this solution was added mercaptoacetic acid (184 mg, 2 mmol) followed by additional triethylamine (0.28 mL, 2.0 mmol). The reaction mixture was stirred for 3 min and the resulting suspension was stored at –20 °C for 15 h. The reaction mixture was then warmed to room temperature, diluted with saturated sodium bicarbonate (3 mL) and methanol (2 mL) and purified by reverse phase column chromatography using 10-50% methanol/water to give pure product (196 mg, 64%) as a yellow powder. ^{1}H NMR (DMSO, 500 MHz): δ 10.82 (bs, 1H), 9.37 (bs, 1H), 9.11 (s, 1H), 8.62 (s, 1H), 8.59 (d, J = 8.2 Hz, 1H), 8.52 (s, 1H), 8.43 (s, 1H), 8.26 (s, 1H), 7.89-7.84 (m, 3H), 7.74 (d, J = 8.4Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.36 (m, 2H), 7.22 (d, J = 4.4 Hz, 1H), 7.17 (d, J = 7.0 Hz, 1H), 5.00 (d, J = 12.1 Hz, 1H), 5.74 (m, 1H), 5.68 (d, J = 8.6Hz, 1H), 5.22 (d, J = 7.4 Hz, 1H), 5.07 (m, 1H), 5.03 (d, J = 12.5 Hz, 1H), 4.93 (d, J = 4.6 Hz, 1H), 4.76 (d, J = 10.2 Hz, 1H), 4.60 (m, 1H), 4.54 (d, J = 11.1 Hz, 1H), 4.31 (d, J = 9.6Hz, 1H),

4.26 (m, 1H), 4.13 (d, J = 10.4 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.93-3.89 (m, 4H), 3.75 (d, J = 8.5 Hz, 1H), 3.27-3.17 (m, 6H), 3.12-3.09 (m, 1H), 3.02-2.98 (m, 1H), 2.89 (m, 3H), 2.54 (m, 1H), 2.04 (s, 1H), 1.99 (s, 3H), 1.95 (m, 1H), 1.78 (d, J = 14.0 Hz, 1H), 1.41 (s, 3H), 1.16 (m, 2H), 1.10 (m, 4H), 0.56 (d, J = 6.6 Hz, 3H). MS: 1529.4 $(M+H)^+$, 1527.5 $(M-H)^-$; HRMS (ES) calcd. for $C_{63}H_{65}N_{14}O_{20}S_6$ $(M+H)^+$: 1529.282, found: 1529.282. Anal. Calcd. for $C_{63}H_{64}N_{14}O_{20}S_6Na \bullet 9H_2O$: C, 46.14; H, 4.47; N, 11.96; S, 11.73. Found: C, 46.17; H, 4.49; N, 11.80; S, 11.15.

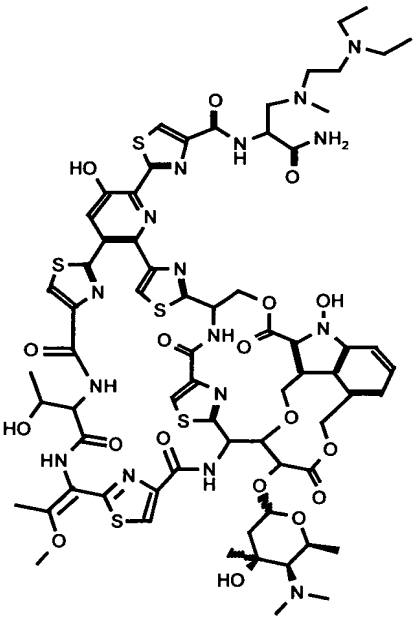
EXAMPLE 5



A suspension of Nocathiacin I (0.29g, 0.2 mmol) in deionized water was treated with 1-(3-aminopropyl)imidazole (0.24 mL, 2.0 mmol). The solution was stirred for 3-4 minutes then stored at -20°C for 16 hours. The reaction was diluted with water (total volume 40 mL) and quenched by addition of TFA (to pH 3.1). The product was purified by chromatography on C-18, using 3:10 Acetonitrile/H_2O + 0.1%TFA as eluent. The lyophilized product was dissolved in H_2O and passed through chloride ion exchange resin to afford the product (0.195 g, 0.125 mmol, 63%) as a yellow lyophilized solid: ^1H NMR (DMSO-d_6, 500MHz) δ 10.98

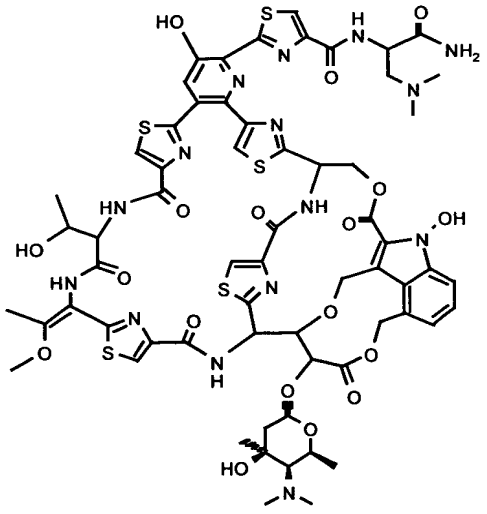
(d, J = 10.5, 1H), 10.77 (bs, 1H), 9.60 (bs, 1H), 9.42 (m, 1H), 9.13 (s, 1H), 8.78 (bs, 1H), 8.66 (s, 1H), 8.59 (s, 2H), 8.54 (m, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.92-7.82 (m, 3H), 7.74 (d, J = 8.4, 1H), 7.53 (bs, 1H), 7.35 (m, 2H), 7.19 (d, J = 7.0, 1H), 6.40 (bs, 1H), 6.02 (d, J = 12.2, 1H), 5.76 (q, J = 11.0, 4.0, 1H), 5.72 (d, J = 9.2, 1H), 5.22 (m, 1H), 5.06 (m, 3H), 4.96 (m, 1H), 4.79 (d, J = 10.4, 1H), 4.52 (d, J = 11.3, 1H), 4.30 (d, J = 9.6, 1H), 4.25 (t, J = 5.6, 1H), 4.15 (d, J = 10.7, 1H), 4.05 (d, J = 6.6, 1H), 3.91 (s, 3H), 3.89 (m, 1H), 3.67 (m, 1H), 3.51 (t, J = 10, 1H), 3.12 (bs 1H), 2.9-2.7 (m, 12H), 2.4 (m, 1H), 2.13 (m, 1H), 2.00 (s, 2H), 1.94 (d, J = 14.7, 1H), 1.61 (s, 3H), 1.15 (bs, 3H), 0.80 (d, J = 6.8, 3H); MS: 1562.2 $(M+H)^+$, 1560.2 $(M-H)^-$; Anal. Calcd for $C_{67}H_{71}N_{17}O_{18}S_5 \bullet 3.3\ HCl \bullet 6.7\ H_2O$: C,44.61 ; H, 4.90; N, 13.20; S, 8.89; Cl, 6.49. Found: C, 44.63; H, 4.93; N, 13.06; S, 9.00; Cl, 6.59.

EXAMPLE 6



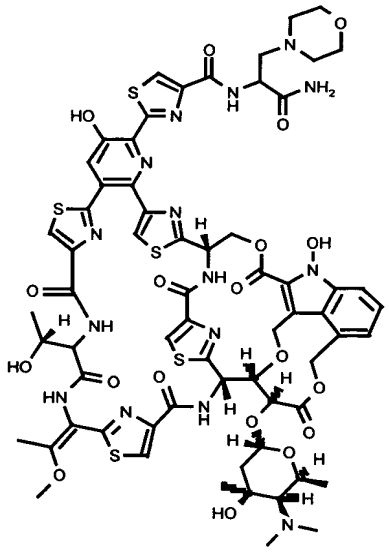
Following the procedure as described for Example 5 except using N,N-Diethyl-N'-(methyl)ethylenediamine (0.32 mL, 2.0 mmol) as the amine component, to afford the product (0.140 g, 0.089 mmol, 45%) as a yellow lyophilized solid: ^{1}H NMR (DMSO-d_6, 300MHz) δ 10.95 (m, 1H), 10.79 (bs, 1H), 9.40 (bs, 1H), 9.12 (s, 1H), 8.78 (bs, 1H), 8.64 (s, 1H), 8.57 (m, 2H), 8.52 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.92-7.82 (m, 2H), 7.73 (d, J = 8.4, 1H), 7.52 (bs, 1H), 7.34 (m, 2H), 7.17 (d, J =7.0, 1H), 6.39 (bs, 1H), 6.01 (d, J = 11.8, 1H), 5.74 (m, 1H), 5.70 (d, J = 9.5, 1H), 5.20 (m, 1H), 5.03 (m, 3H), 4.78 (d, J = 9.5, 1H), 4.51 (d, J = 11.0, 1H), 4.29 (d, J = 9.5, 1H), 4.25 (t, J = 6.1, 1H), 4.13 (d, J = 10.3, 1H), 4.05 (d, J = 8.7, 1H), 3.90 (s, 3H), 3.89 (m, 1H), 3.70 (m, 1H), 3.12 (m, 4H), 2.9-2.7 (m, 10H), 2.4 (m, 1H), 2.10 (m, 1H), 1.98 (s, 3H), 1.93 (m, 1H), 1.59 (s, 3H), 1.25-1.0 (m, 9H), 0.78 (d, J = 6.7, 3H); Anal. Calcd for $C_{68}H_{78}N_{16}O_{18}S_5 \bullet 3.25$ HCl $\bullet$ 6.5 H_2O: C, 45.29; H, 5.27; N, 12.43; S, 8.89; Cl, 6.39. Found: C, 45.44; H, 5.17; N, 12.46; S, 8.42; Cl, 6.33.

EXAMPLE 7



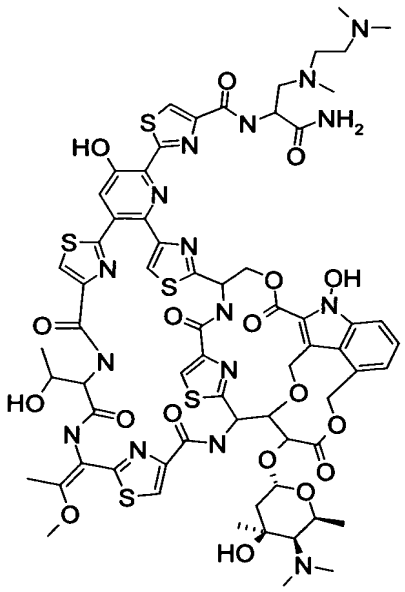
Following the procedure as described for Example 5 except using N,N-Dimethylamine (0.25 mL, 2.0 mmol) as the amine component, to afford the product (0.160 g, 0.108 mmol, 53%) as a yellow lyophilized solid: ^{1}H NMR (DMSO-d_6, 500MHz) δ 10.94 (d, J = 9.5,1H), 10.77 (bs, 1H), 9.39 (m, 2H), 9.12 (s, 1H), 8.66 (m, 2H), 8.58 (s, 1H), 8.54 (s, 1H), 8.23 (s, 1H), 8.05 (d, J = 2.5, 1H), 7.93-7.80 (m, 3H), 7.75 (d, J = 8.2, 1H), 7.54 (bs, 1H), 7.36 (m, 2H), 7.19 (d, J =6.7, 1H), 6.39 (bs, 1H), 6.03 (d, J = 12.5, 1H), 5.75 (m, 1H), 5.71 (d, J = 8.9, 1H), 5.22 (m, 1H), 5.05 (m, 3H), 4.96 (m, 1H), 4.79 (d, J = 10.4, 1H), 4.52 (d, J = 10.7, 1H), 4.30 (d, J = 9.8, 1H), 4.25 (t, J = 6, 1H), 4.15 (d, J = 10.7, 1H), 4.04 (d, J = 9.2, 1H), 3.91 (s, 3H), 3.88 (m, 1H), 3.66 (m, 1H),3.49 (t, J = 11, 1H) 3.12 (bs, 1H), 2.9-2.6 (m, 13H), 2.46 (bs, 1H), 2.12 (m, 1H), 1.99 (s, 3H), 1.94 (d, J = 14.7, 1H), 1.60 (s, 3H), 1.16 (bs, 3H), 0.81 (d, J = 6.7, 3H); MS: 1482 (M+H)+; HRMS (ES) found: 1482.34590; Anal. Calcd for $C_{63}H_{67}N_{15}O_{18}S_5 \bullet$ 2.25 HCl • 7.0 H_2O: C, 44.75; H, 4.96; N, 12.43; S, 9.48; Cl, 4.72. Found: C, 44.96; H, 4.87; N, 12.48; S, 9.30; Cl, 6.59.

EXAMPLE 8



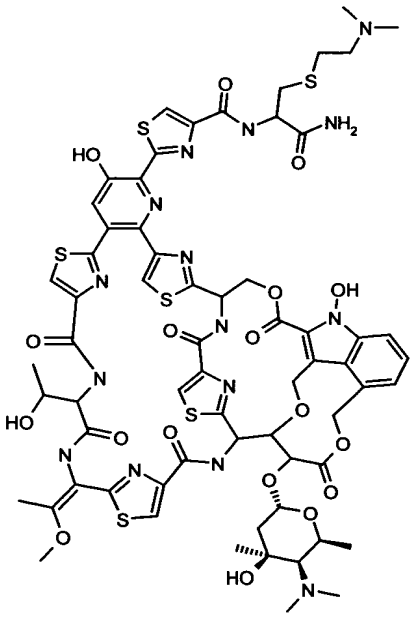
Following the procedure for Example 5 except using nocathiacin I (0.5 mmol, 0.719 g.), and morpholine (0.87 mL, 10.0 mmol) as the amine component, to afford the product (0.345 g, 0.224 mmol, 43%) as a yellow lyophilized solid: ^{1}H NMR (DMSO-d_6, 500MHz) δ 10.98 (m, 1H), 10.79 (bs, 1H), 9.46 (bs, 1H), 9.12 (s, 1H), 8.75 (bs, 1H), 8.65 (s, 1H), 8.58 (m, 2H), 8.54 (s, 1H), 8.22 (s, 1H), 8.05 (s, 1H), 7.92-7.82 (m, 2H), 7.74 (d, J = 8.4, 1H), 7.52 (bs, 1H), 7.34 (m, 2H), 7.19 (d, J =7.1, 1H), 6.39 (bs, 1H), 6.02 (d, J = 12.1, 1H), 5.75 (m, 1H), 5.71 (d, J = 10.0, 1H), 5.23 (m, 1H),5.07-4.90 (m, 3H), 4.78 (d, J = 10.3, 1H), 4.62 (d, J = 10.7, 1H), 4.30 (d, J = 9.6, 1H), 4.25 (t, J = 5.5, 1H), 4.14 (d, J = 10.5, 1H), 4.05 (d, J = 8.7, 1H), 3.97 (m, 1H), 3.91 (s, 3H), 3.78 (m, 2H), 3.22 (bs, 2H), 3.12 (bs, 1H), 2.89 (m, 7H), 2.47 (bs, 1H), 2.13 (m, 1H), 2.00 (s, 3H), 1.93 (d, J = 14.7, 1H), 1.61 (s, 3H), 1.15 (bs, 3H), 0.81 (d, J = 7.0, 3H); MS: 1524.5 $(M+H)^+$, 1522.6 $(M-H)^-$; Anal. Calcd for $C_{65}H_{69}N_{15}O_{19}S_5 \bullet 2.5$ HCl $\bullet$ 5.8 H_2O: C, 45.38; H, 4.87; N, 12.21; S, 9.32; Cl, 5.15. Found: C, 45.11; H, 4.71; N, 12.15; S, 9.25; Cl, 5.19.

EXAMPLE 9



Following the procedure as described for Example 5 except using N,N,N'-Trimethylethylenediamine (0.26 mL, 2.0 mmol) as the amine component, to afford the product (0.135 g, 0.088 mmol, 44%) as a yellow lyophilized solid: ^{1}H NMR (DMSO-d_6, 300MHz) δ 10.96 (bs, 1H), 10.79 (bs, 1H), 9.12 (s, 1H), 8.75 (bs, 1H), 8.64 (s, 1H), 8.57 (m, 2H), 8.52 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.92-7.82 (m, 2H), 7.73 (d, J = 8.5, 1H), 7.34 (m, 2H), 7.17 (d, J =6.7, 1H), 6.38 (bs, 1H), 6.01 (d, J = 11.9, 1H), 5.74 (m, 1H), 5.70 (d, J = 9.2, 1H), 5.20 (m, 1H), 5.04 (m, 3H), 4.77 (d, J = 9.1, 1H), 4.51 (d, J = 11.1, 1H), 4.29 (d, J = 9.6, 1H), 4.24 (m, 1H), 4.13 (d, J = 10.6, 1H), 4.04 (d, J = 9.8, 1H), 3.90 (s, 3H), 3.88 (m, 1H), 3.10 (s, 1H), 2.9-2.7 (m, 10H), 2.4 (m, 1H), 2.10 (m, 1H), 1.98 (s, 3H), 1.93 (m, 1H), 1.59 (s, 3H), 1.3 (m, 3H), 0.78 (d, J = 7.1, 3H); MS: 1540.4 $(M+H)^+$, 1537.5 $(M-H)^-$; Anal. Calcd for $C_{66}H_{74}N_{16}O_{18}S_5 \bullet 3.25\ HCl \bullet 7.4\ H_2O$: C, 44.25; H, 5.18; N, 12.51; S, 8.95; Cl, 6.43. Found: C, 44.64; H, 4.80; N, 12.64; S, 8.76; Cl, 6.85.

EXAMPLE 10



To a stirred suspension of Nocathiacin I (287.5 mg, 0.2 mmol) in water (10 mL) was added triethylamine (0.34 mL, 2.43 mmol) and stirred until the reaction mixture became a clear yellow solution. To this solution was added 2-(N,N-dimethylamino)ethanethiol hydrochloride (284 mg, 2 mmol), stirred for 3 min and left at –20 °C for 2.5 h. The reaction mixture was then warmed to room temperature, diluted with 1 M aqueous HCl (3 mL) and water (20 mL) and purified by reverse phase column chromatography on C-18 using 10-80% methanol/water containing about 0.01% HCl to provide pure product (277 mg, 87%) as a yellow powder. MS: 1542.6 $(M+H)^+$, 1540.6 $(M-H)^-$; HRMS: found 1542.354.

EXAMPLES 11-56, 58-92

Examples 11-56 and 58-92 were prepared according to either Method A or Method B as described directly below.

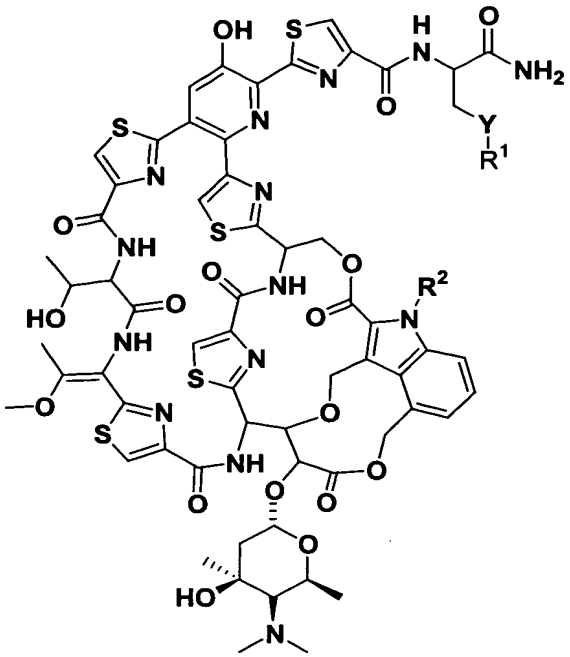
Method A, General procedure for the Michael addition of amines to a Nocathiacin:

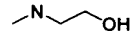
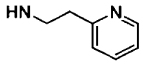
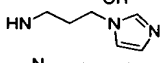
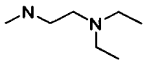
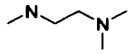
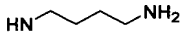
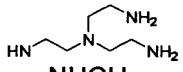
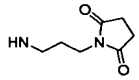
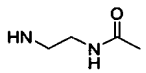
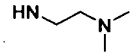
The following general procedure was used to prepare the compounds of examples 11-33, 35-39, 41, 48-59, 61, 63-79 and 81-92 with the exception that the Nocathiacin in which R^2 is H was used as starting material for example 92. To a stirred solution of an appropriate amine of general formula $HNRR^1$ (3.50 mmol,10 equivalents) in water (17.5 mL) at room temperature was added Nocathiacin I (0.5 g, 0.35 mmol,1 equivalent). The reaction mixture was stirred for 3 to 5 minutes until it became a clear homogeneous solution. If the reaction did not become a clear homogeneous solution then triethylamine (0.70-1.40 mmol, 2-4 equivalents) was added. The reaction mixture was then maintained at –20 °C for a period of 3 to 20 h. The reaction mixture was then worked up and the product purified by one of the following methods:

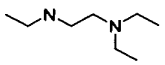
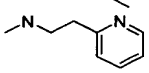
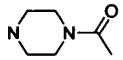
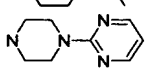
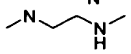
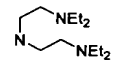
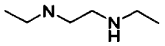
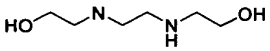
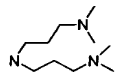
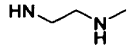
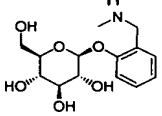
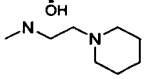
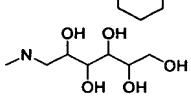
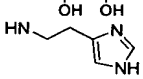
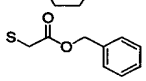
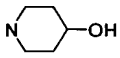
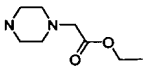
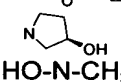
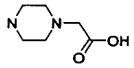
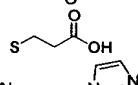
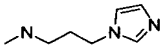
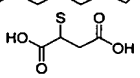
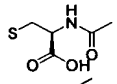
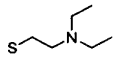
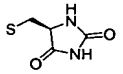
a) reaction quenched with 1N aqueous hydrochloric acid and subjected to medium pressure chromatography, as described above; b) reaction quenched with trifluoroacetic acid and subjected to preparative HPLC or medium pressure chromatography on C-18; or c) the reaction mixture directly subjected to medium pressure chromatography or preparative HPLC. Examples 73 and 74 were isolated as single diastereomers (the stereochemistry of the carbon to which $-CH_2YR^1$ is attached is denoted (R) or (S) in the following table) from the same reaction mixture by preparative HPLC. Examples 75 and 76 were also isolated as single diastereomers by the same method. The product containing fractions were concentrated under reduced pressure, frozen and lyophilized to afford the product as a yellow powder.

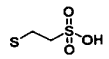
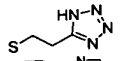
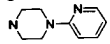
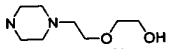
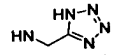
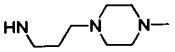
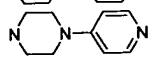
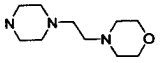
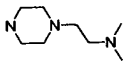
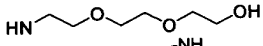
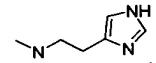
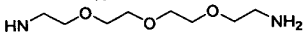
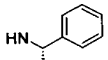
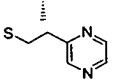
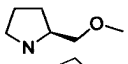
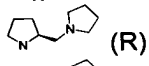
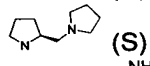
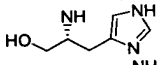
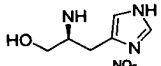
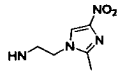
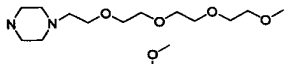
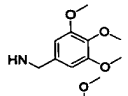
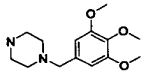
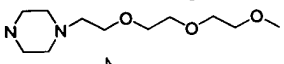
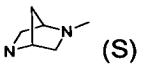
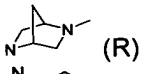
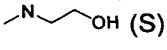
Method B: General procedure for the Michael addition of thiols to a Nocathiacin:

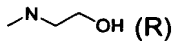
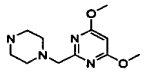
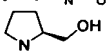
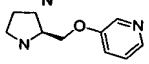
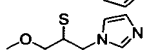
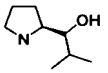
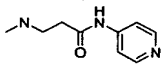
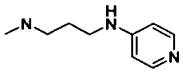
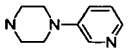
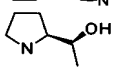
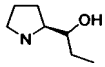
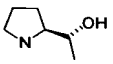
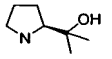
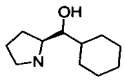
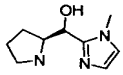
The following general procedure was used to prepare the compounds of examples 34, 40, 42-47, 60, 62 and 80. To a stirred solution of triethylamine (12.5 equivalents) in water (17.5 mL) at room temperature was added Nocathiacin I (0.5 g, 0.35 mmol,1 equivalent). To this was added an appropriate thiol of general formula HSR^1 (3.50 mmol,10 equivalents). The reaction mixture was stirred for 3 to 5 minutes until it became a clear homogeneous solution. If the reaction did not become a clear homogeneous solution then additional triethylamine (0.70-1.40 mmol, 2-4 equivalents) was added. The reaction mixture was then maintained at –20 °C for a period of 3 to 20 h. The reaction mixture could then be purified by procedures analogous to those described for Method A, above.

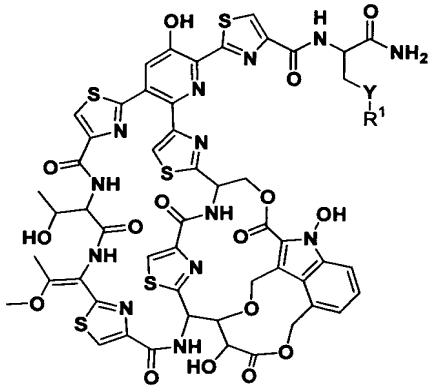


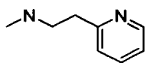
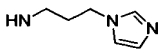
Example Number	R^2	$Y-R^1$	MS observed $(M+H)^+$	MS observed $(M-H)^-$	HRMS observed
1	OH		1538.1	1535.54	1537.390
2	OH		1512.4	1511.60	1512.359
3	OH		1559.7	1558.46	1559.374
4	OH		1529.4	1527.47	1529.282
5	OH		1562.2	1560.17	
6	OH		1567.5	1565.6	
7	OH	$N(CH_3)_2$	1482		1482.34590
8	OH		1524.5	1522.59	
9	OH		1540.4	1537.5	
10	OH		1542.6	1540.65	1542.354
11	OH		1525		1525.39048
12	OH		1583		1583.44636
13	OH	$NHCH_3$	1468.6	1466.53	
14	OH		1579.1	1578.18	
15	OH		1508.4	1507.65	1508.364
16	OH		1539.2	1537.4	1539.366
17	OH		1525.7	1523.2	
18	OH	NHOH	1471.3	1468.9	

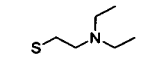
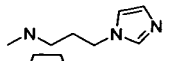
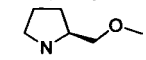
19	OH		1567.5	1565.6	
20	OH		1573.5	1571.60	1573.387
21	OH		1565.5	1563.86	1565.386
22	OH		1601.6	1600.86	1601.401
23	OH		1525.5	1524.3	
24	OH		1652.7	1650.8	
25	OH		1553.6		
26	OH		1585.7	1584.1	
27	OH		1624.6	1623.2	
28	OH		1511.5	1509.7	
29	OH		1736.1		1736.429
30	OH		1579.8	1579.00	1579.436
31	OH		1632.7	1630.71	1632.399
32	OH		1548.7	1546.84	1548.367
33	OH		1542.2		1542.367
34	OH		1619.1		1619.331
35	OH		1539.8	1537.68	1538.375
36	OH		1609.7	1608.23	1609.412
37	OH		1525.7	1523.68	1524.355
38	OH	HO-N-CH_3	1484.2		
39	OH		1581.7	1579.73	1581.375
40	OH		1543.5	1541.62	1543.302
41	OH		1576.8	1574.85	1576.402
42	OH		1587.4	1585.51	1587.284
43	OH		1600.5	1598.53	1600.317
44	OH		1570.6	1568.67	1570.386
45	OH		1583.7	1581.70	1583.301

46	OH		1579.5	1577.62	1579.266
47	OH		1567.4	1565.59	1567.319
48	OH		1600.7	1598.74	1600.404
49	OH		1611.3		1611.422
50	OH		1536.3		1536.345
51	OH		1594.5		1594.443
52	OH		1600.8		1600.400
53	OH		1636.9	1634.96	1636.455
54	OH		1596		
55	OH		1586.8	1584.86	1586.393
56	OH		1562.7	1560.79	
58	OH		1629.6	1627.74	1629.437
59	OH		1551.8	1549.89	1551.404
60	OH		1580.6	1578.67	1580.363
61	OH		1558.3		1558.374
62	OH		1577.6	1575.71	1577.329
63	OH		1552.6	1550.76	1552.393
64	OH	 (R)	1591.5		1591.434
65	OH	 (S)	1591.5		1591.431
66	OH		1578.4	1576.74	1578.378
67	OH		1579.8	1576.63	1578.383
68	OH		1607.6	1605.54	1607.365
69	OH		1713.5		1713.496
70	OH		1635		1634.392
71	OH		1704		1703.447
72	OH		1669.8	1667.9	1669.463
73	OH	 (S)	1549.7	1547.68	1549.391
74	OH	 (R)	1549.6	1547.71	1549.385
75	OH	 (S)	1513.1	1510.76	

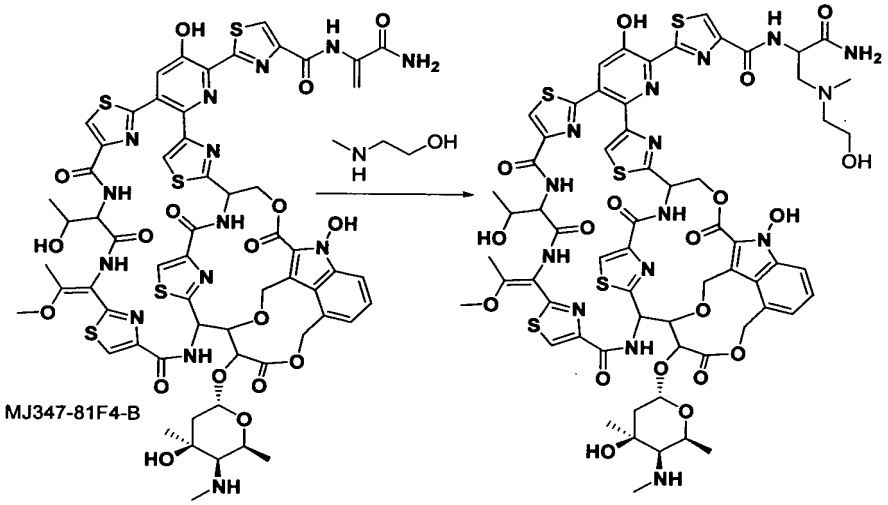
76	OH		1512.6	1510.65	
77	OH		1675.5		1675.429
78	OH		1538.6	1536.56	1538.374
79	OH		1616.1	1613.65	1615.404
80	OH		1609.6	1607.56	1609.355
81	OH		1580.6	1578.84	1580.418
82	OH		1617.3	1614.64	
83	OH		1604.1	1601.98	
84	OH		1524.7	1523.96	
85	OH		1600.3		1600.400
86	OH		1553.7	1550.92	1552.391
87	OH		1566.3		
88	OH		1552.6	1550.74	1552.387
89	OH		1566.6	1565.62	1566.405
90	OH		1620.7	1619.78	1620.452
91	OH		1619.7	1617.75	1618.409
92	H		1494.4	1496.7	



Example	Y-R^1	(M+H)$^+$	(M-H)$^-$	HRMS if available
93		1402.3	1401.29	1402.2667
94		1391.4	1389.6	1391.262
95		1358.2	1356.3	1358.159

96		1355.3	1353.2	1355.247
97		1405.6	1403.49	1405.278
98		1382.5	1379.43	

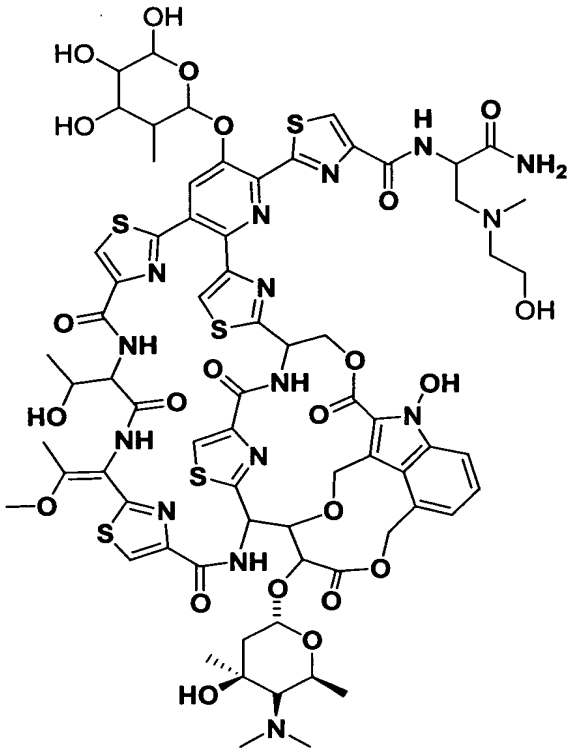
EXAMPLE 99



To a stirred solution of 2-(Methylamino)ethanol (11 mg, 0.15 mmol,10 equivalents) in water (1.0 mL) at room temperature was added the compound MJ347-81F4-B (20.5 mg,1 equivalent). The reaction mixture was stirred for 3 to 5 minutes until it became a clear homogeneous solution then was maintained at –20 °C for 16 h. The reaction mixture was then subjected to preparative HPLC. The product fraction was concentrated *in vacuo*, frozen and lyophilized to provide the bis trifluoroacetic acid salt of the product as a yellow solid.

Calcd. Mass for $C_{63}H_{67}N_{15}O_{19}S_5$ is1497.334. Found MS: 1498.4 $(M+H)^+$, 1496.61 $(M-H)^-$; HRMS: 1498.344.

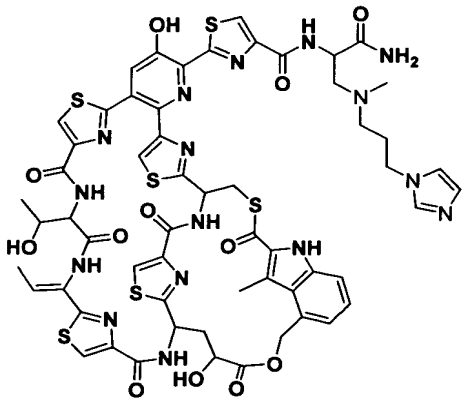
EXAMPLE 100



To a suspension of the appropriate nocathiacin derivative (52 mg) in water (5 mL) was added 2-(Methylamino)ethanol. The mixture was stirred for 5 minutes at room temperature and became a yellowish green solution. The mixture was then maintained at –20 °C for 20 h. The mixture was then purified by reverse phase column chromatography on C-18 using 10-80% acetonitrile/water containing about 0.01% HCl to provide the bis hydrochloride salt of the product as a yellow solid.

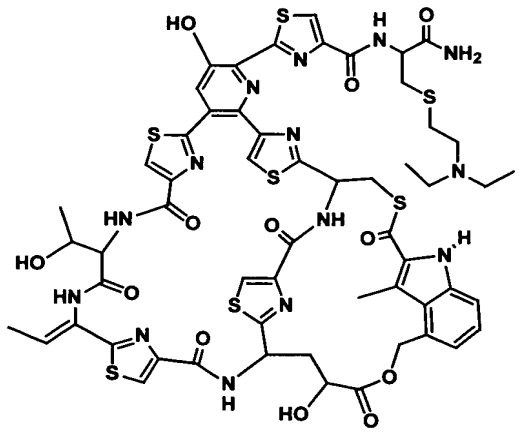
Calcd. Mass for $C_{70}H_{79}N_{15}O_{23}S_5$ is1657.82. Found MS: 1658.9 $(M+H)^+$, 1657.18 $(M-H)^-$.

EXAMPLE 101



To a stirred solution of nosiheptide (69 mg, 0.056 mmol) in water (3 mL) and DMF (1 mL) was added 1-(3-N-methylaminopropyl)imidazole (140 mg, 1 mmol) and the resulting dark solution was left for 3 days at –20 °C. The reaction mixture was then allowed to warm to room temperature, diluted with methanol and purified by preparative HPLC to provide the bis trifluoroacetic acid salt of the product (4.0 mg, 5%) as a yellow powder. Calcd. Mass for $C_{58}H_{57}N_{16}O_{12}S_6$ is 1361.267. Found MS: 1361.9 $(M+H)^+$, 1359.4 $(M-H)^-$; HRMS: Found 1361.269 $(M+H)^+$.

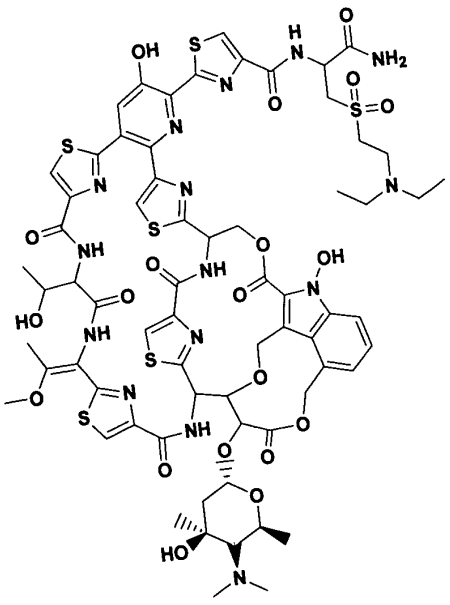
EXAMPLE 102



To a stirred suspension of nosiheptide (61.12 mg, 0.05 mmol) and 2-(N,N-diethylamino)ethanethiol hydrochloride (42.43 mg, 0.25 mmol) in

water (5 mL) was added triethylamine (70 μL, 0.5 mmol) and stirred for 15 minutes at room temperature. To the resulting suspension DMF (3 mL) was added, stirred for 5 minutes and the clear yellow solution was left at – 20 °C for 20 h. The reaction mixture was then allowed to warm to room temperature, diluted with methanol and purified by preparative HPLC to provide the bis trifluoroacetic acid salt of the product as a yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6): 10.85 (d, J = 4.2 Hz,1H), 9.41 (bs, 1H), 9.24 (d, J = 8.7 Hz, 1H), 9.05 (bs, 1H), 8.69 (bs, 1H), 8.55 (s, 1H), 8.44 (bs, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 7.93 (t, J = 3.1 Hz, 1H), 7.90 (s, 1H), 7.78 (d, J = 9.4 Hz, 1H), 7.65 (s, 1H), 7.54 (bs, 1H), 7.33 (s, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.0 Hz, 1H), 6.47 (q, J = 6.8, 13.7 Hz, 1H), 5.86 (bs, 1H), 5.71 (bs, 1H), 5.58-5.55 (m, 2H), 4.68 (m, 2H), 4.58 (bs, 1H), 4.08 (d, J = 12.3 Hz, 2H), 3.85-3.81 (m, 2H), 3.53 (bs, 2H), 3.28-3.13 (m, 9H), 2.98-2.88 (m, 4H), 2.71-2.55 (m, 2H), 2.54 (s, 1H), 1.72 (d, J = 6.75 Hz, 4H), 1.20-1.16 (m, 8H); Calcd. $(M+H)^+$ (ESI) for $C_{57}H_{58}N_{14}O_{12}S_7$: 1355.248, found: 1355.247.

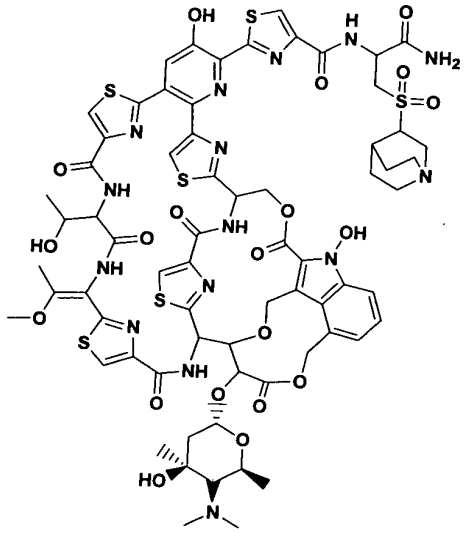
EXAMPLE 103



To a stirred solution of the compound of example 44 (as the hydrochloride salt, 336 mg, 0.19 mmol) in water (40 mL) was added

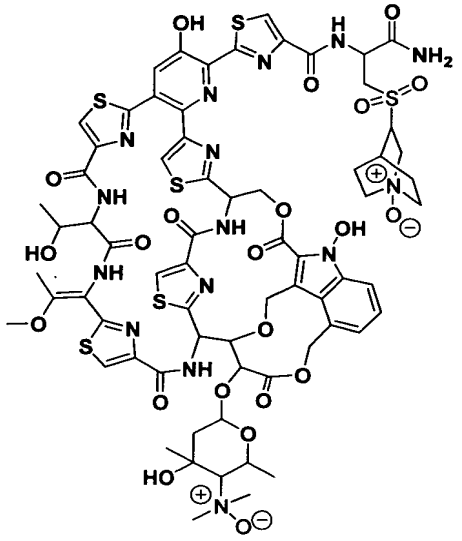
sodium tungstate dihydrate (15 mg, 0.045 mmol) followed by 30% aqueous hydrogen peroxide (1 mL) at room temperature. After 3 h, the reaction mixture was purified by reverse phase column chromatography on C-18 using 10-80% methanol/water containing about 0.01% HCl to provide pure product (232 mg, 68%) as a yellow powder. MS: 1603.0 $(M+H)^+$, 1600.6 $(M-H)^-$; HRMS: found 1602.372.

EXAMPLE 104



Example 104 was prepared by the same method as described for Example 103 starting from the compound of Example 60 (as the hydrochloride salt) to provide the product as a yellow powder. MS: 1613.5 $(M+H)^+$, 1611.5 $(M-H)^-$; HRMS: found 1612.354.

EXAMPLE 105



To a solution of the compound of example 60 (as the free base,116.0 mg, 0.07 mmol) in water (10 mL) was added sodium tungstate dihydrate (5 mg, 0.015 mmol) followed by 30% hydrogen peroxide (0.5 mL). The reaction mixture was stirred at room temperature 3 hours then was purified by reverse phase column chromatography on C-18 using 10-80% methanol/water containing about 0.01% HCl to provide pure product as a yellow powder. MS: $(M+H)^+$ 1645.9, $(M-H)^-$ 1642.80; HRMS: found 1644.344; Anal. Calcd for $C_{68}H_{73}N_{15}O_{22}S_6 \bullet 2.0$ HCl $\bullet$ 10.0 H_2O: C, 43.04; H, 5.05; N, 11.07; S, 10.14; Cl, 3.74. Found: C, 42.50; H, 4.89; N, 10.80; S, 9.92; Cl, 3.73.

EXAMPLES 106-111

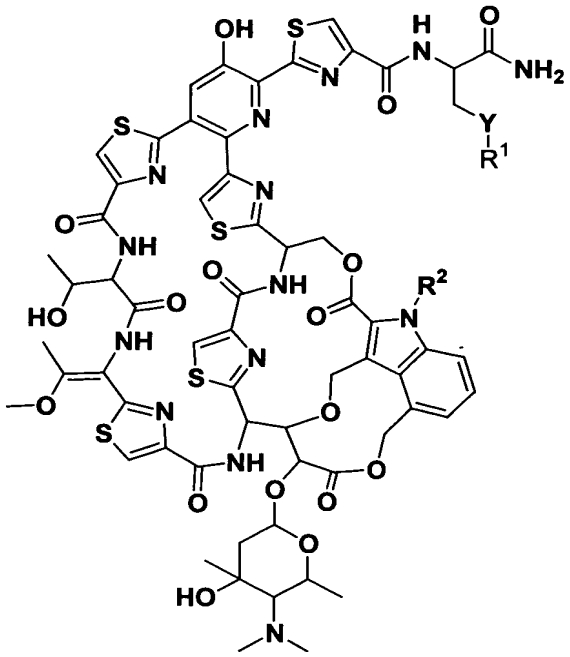
Examples 106-109 were prepared according to the following general procedure for the preparation of amides and ureas of Michael adducts:

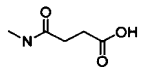
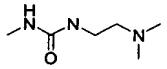
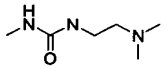
To a stirred solution of appropriate amine (10 equiv.) in water at room temperature was added Nocathiacin I (1 equiv.). The reaction

mixture was stirred for 3-5 minutes until it became a clear homogeneous solution. Then the reaction mixture was maintained at –20 °C for 16 h. An appropriate acid anhydride or isocyanate (10 equiv.) was then added to the reaction mixture and the mixture was allowed to warm to room temperature. Once the reaction was done as judged by analytical HPLC analysis, it was purified by preparative HPLC to afford the compounds of examples 106-109 (as shown in the table below) as a yellow powder. For examples 106-109, methylamine (40 weight % solution in water) was employed as the amine component. For examples 106 and 107 the anhydride component employed was succinic anhydride and acetic anhydride, respectively. Examples 108 and 109 were obtained from the reaction employing methyl isocyanate as the isocyanate component.

Examples 110 and 111 were prepared according to the following procedure:

To a solution of the compound of example 17 (77 mg, 0.05 mmol) in pyridine (1 mL) and DMF (0.5 mL) at room temperature was added methyl isocyanate (3 μL, 0.05 mmol). The reaction mixture was stirred at room temperature for approximately 1 hour then was concentrated *in vacuo*. The residue was dissolved in DMF (1.7 mL) and was purified by preparative HPLC according to the general method to provide two product components. The earlier eluting component was found to be the compound designated example 111 and the later eluting component was found to be the compound designated example 110.



Example	R^2	Y-R^1	$(M+H)^+$	$(M-H)^-$	HRMS if available
106	OH		1568.3		1568.348
107	$CH_3C(O)O$	CH_3CONCH_3	1552.6	1551.7	1552.350
108			1582.4	1580.52	1582.3752
109	OH		1525.3		1525.357
110	OH		1582.4	1579.9	
111			1639.3	1638.0	

Biological Activity

In vitro Antibiotic Activity of Formula I Compounds:

To demonstrate its antimicrobial properties, the minimum inhibitory concentration (MIC) for compounds of the invention was obtained against a variety of bacteria using a conventional broth micro dilution assay in accordance with standards recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The serial broth dilution method

used Mueller-Hinton medium except for the *Streptococcus pneumoniae* which was tested in 50% Mueller-Hinton medium and 50% Todd Hewitt medium. The final bacterial inoculate contained approximately 5 x 10^5 cfu/well and was run on microtiter plates. The volume of each well was 100 μL and the plates were incubated at 35 °C for 18 hours in ambient air. The MIC was defined as the lowest drug concentration that prevented visible growth. Some of the results obtained are shown in Table 1 below, and demonstrate that compounds of this invention have utility in treating bacterial infections. Column 1 of Table 1 provides the compound example number and columns 2, 3, and 4 provide the MIC obtained by that compound against the specified strain of organism.

Table 1

EXAMPLE number	MIC (μg/mL) against *Staphylococcus aureus* A15090	MIC (μg/mL) against *Streptococcus pneumoniae* A28272	MIC (μg/mL) against *Enterococcus faecalis* A20688
1	0.25	0.125	0.5
2	0.015	0.015	0.06
3	1.0	0.25	1.0
4	2.0	0.125	2.0
5	1.0	0.03	1.0
6	0.125	0.03	2.0
7	0.06	0.03	0.125
8	0.015	0.003	0.125
9	0.06	0.007	0.5
10	0.125	0.015	0.25
11	2.0	0.5	8.0
12	2.0	0.5	4.0

13	2.0	0.001	8.0
14	1.0	0.06	1.0
15	0.06	0.015	0.5
16	1.0	0.125	4.0
17	2.0	0.03	4.0
18	0.5	0.03	4.0
19	0.25	0.03	1.0
20	0.125	0.005	0.25
21	0.5	0.03	2.0
22	0.5	0.0005	1.0
23	0.06	0.001	0.5
24	1.0	0.007	2.0
25	1.0	0.0005	2.0
26	1.0	0.001	2.0
27	4.0	0.0005	2.0
28	0.25	0.03	0.5
29	0.06	0.015	0.25
30	0.125	0.03	1.0
31	0.125	0.125	1.0
32	0.25	0.125	4.0
33	0.125	0.015	0.25
34	1.0	0.001	1.0
35	0.06	0.007	0.25
36	0.06	0.007	0.25
37	0.06	0.007	0.125
38	0.03	0.007	0.06
39	1.0	0.03	1.0
40	1.0	0.03	(4.0)
41	0.5	0.125	0.5
42	4.0	0.25	4.0
43	2.0	0.125	8.0

44	0.125	0.015	0.25
45	4.0	0.03	128
46	4.0	0.06	128
47	2.0	0.25	32
48	0.125	0.03	0.25
49	0.5	0.5	2.0
50	0.25	0.25	1.0
51	0.25	0.015	4.0
52	0.5	0.5	1.0
53	0.5	0.5	1.0
54	0.5	0.25	0.125
55	0.25	0.06	0.5
56	0.25	0.125	0.5
58	1.0	0.25	1.0
59	1.0	0.25	2.0
60	2.0	0.5	2.0
61	0.25	0.03	0.25
62	0.125	0.015	0.25
63	0.125	0.03	0.25
64	0.06	0.003	1.0
65	0.03	2.0	1.0
66	2.0	2.0	16
67	2.0	1.0	8.0
68	2.0	0.5	8.0
69	0.5	0.25	4.0
70	0.25	0.06	4.0
71	1.0	0.5	2.0
72	4.0	0.5	4.0
73	0.25	0.015	2.0
74	0.5	0.015	2.0
75	0.06	0.007	0.25

76	0.06	0.007	0.25
77	0.125	0.015	0.5
78	0.03	0.007	0.125
79	0.06	0.001	0.125
80	0.25	0.03	0.125
81	0.125	0.007	0.125
82	0.5	0.03	0.5
83	1.0	0.25	0.5
84	0.5	0.125	0.25
85	0.06	0.007	0.25
86	0.007	0.015	0.06
87	0.015	0.007	0.06
88	0.007	0.03	0.06
89	0.003	0.007	0.03
90	0.03	0.007	0.06
91	0.03	0.015	0.06
92	0.125	0.0005	0.125
93	0.06	0.001	0.06
94	na	na	na
95	0.5	0.03	4.0
96	0.125	0.015	0.25
97	0.125	0.125	0.25
98	0.03	0.003	0.5
99	0.03	0.015	0.125
100	1.0	0.015	1.0
101	0.125	0.003	0.125
102	0.125	0.03	0.25
103	0.06	0.007	0.03
104	0.5	0.06	1.0
105	1.0	0.25	2.0
106	4.0	8.0	32

107	0.03	0.06	1.0
108	0.125	0.03	0.5
109	0.06	0.06	0.5
110	0.5	0.03	2.0
111	1.0	0.06	2.0

In the preceding table na indicates the results were not available.

Formula I compound *in vivo* Antibiotic Activity in a Systemic *Staphylococci aureus* Infection Model:

Many of the compounds of Formula I (Examples 1-111, above) were evaluated for antibiotic activity *in vivo*, in a systemic infection model using female ICR mice. The animals were infected intraperitonially (IP) with 6.5×10^6 CFU of an overnight culture of *Staphylococcus aureus* A15090 suspended in 7% mucin. The compounds of Formula I (such as Examples 1-10, above) were tested at 4 dose levels, (25, 6.25, 1.56, and 0.39 mg/kg) and were prepared in a test formulation consisting of 10% DMSO, 5% Tween 80 and 85% water. A PD_{50} (the dose of drug given which protects 50% of mice from mortality) experiment runs for 5 days. During this time, mortality of mice was checked every day and deaths were recorded. The cumulative mortality at each dose level was used to calculate a PD_{50} value for each compound. Surviving mice were sacrificed at the end of day 5 by CO_2 inhalation. Actual calculation of the PD_{50} was performed with a computer program using the Spearman-Karber procedure. The solution was administered subcutaneously (SC) at 1 and 4 hours post-infection. The in-vivo efficacy, expressed as a PD_{50} value, for compounds of Examples 1-10, when dosed SC, were found to be within the range of 0.6 to 10 mg/kg with the exception of the compound of Example 4 which had a PD_{50} of >10 mg/kg. The compounds of Examples 1-3 and 5-9 were also dosed intravenously (*iv*) one hour post infection as

a single bolus of a solution in D5W (5% dextrose in water) in the same infection model. The compounds were found to have PD_{50}s within the range of 0.19 to 7.3 when *iv* administration was used. The compounds of examples 13, 15, 17, 19, 21-22, 24, 29-30, 33, 35, 37-38, 41, 44, 48-49, 52-56, 59-60, 62-65, 67, 69-82, 84-92, 97, 103 and 107-109 were found to have have PD_{50}s within the range of 0.3 to 10 mg/kg when administered subcutaneously as described above. The compounds of examples 11-12, 14, 16, 23, 25-26, 31-32, 39-40, 42-43, 45-47, 51, 58, 66, 83, 95-96, 102, 105 and 111 were found to have PD_{50}s >10 mg/kg. For the compounds of examples 18, 20, 27-28, 34, 50, 61, 68, 93-94, 98-101, 104, 106 and 110 no PD_{50} data was available.